THE YEAR BOOK *of* MEDICINE

(1954 1955 YEAR BOOK *Series)*

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Departments *of the* Year Book *of* Medicine

Infections

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The Chest

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Metabolism

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PUBLISHER'S NOTE The designation (Series 1954 1955) used on the cover and title page of this volume is to indicate its publication during the series year which begins September 1954 with the publication of the YEAR BOOK OF MEDICINE and ends in May 1955 with the YEAR BOOK OF PATHOLOGY AND CLINICAL PATHOLOGY

The articles abstracted herein are taken from journals received between May 1953 and May 1954

PART I

INFECTIONS

INFECTIONS

PAUL B BEESON MD

PART I

INFECTIONS

ANTIBIOTIC THERAPY

General

Binding of Penicillin in Relation to Its Cytotoxic Action I Correlation between Penicillin Sensitivity and Combining Activity of Intact Bacteria and Cell Free Extracts According to Harry Eagle[1] (Nat l Inst of Health) studies with C^{14} or S^{35} labeled penicillin have demonstrated that the antibiotic is bound and concentrated by bacterial suspensions The amount bound from low concentrations (0 001-0 01µg /ml) was related to the penicillin sensitivity of the strain highly sensitive organisms (e g Streptococcus pyogenes) concentrated the antibiotic as much as 200 fold Bacteria in the logarithmic phase of growth resting organisms and cell free sonic extracts had roughly the same reactivity with penicillin Differences in the amount of penicillin bound by bacteria of varying sensitivity do not therefore rest on differences in permeability of the cell

The study indicates that the widely differing susceptibility to penicillin of a number of bacterial species as well as of strains of the same species is determined by similarly varying reactivity of the cells with the antibiotics Intact bacteria bound and concentrated penicillin in relation to their penicillin sensitivity

The relative non toxicity of penicillin for the mammalian host results from the low reactivity of mammalian cells with penicillin

Two difficulties arise with the concept that the sensitivity of various bacterial cells to penicillin is determined by the degree to which they combine with the antibiotic (1) Penicillin resistant variants of normally sensitive cells produced by serial passage through increasing concentrations of anti

(1) J Expe Med 99 207 226 M 1 1954

biotic sometimes retain an affinity for the antibiotic (2) Bacteria may combine with amounts of penicillin far exceeding those bound at the bactericidal concentration without necessarily dying as a result of that combination Nonmultiplying bacteria combine with penicillin to essentially the same degree as do organisms in the logarithmic phase of growth yet are not killed by that combination When such treated bacteria are resuspended in a penicillin free growth medium they eventually resume multiplication at a normal rate without however having meanwhile released the bound antibiotic Binding of the penicillin does not alone suffice to initiate the bactericidal effort Not only must the antibiotic be bound but the cell must be in a medium that permits active metabolism and the antibiotic must remain constantly present in the surrounding fluid

Although treatment of resting cells with penicillin does inactivate one or more vital cell components when the treated but still viable cells are placed in a suitable penicillin free medium they may quickly resynthesize sufficient materials for survival and growth either from the medium itself or from intracellular stores of precursor substances In the presence of penicillin the vital components are inactivated as fast as they are formed and continued absence of the vital components leads to ultimate loss of viability of the cell To die the bacteria would have to be exposed to the antibiotic during active metabolism

Conceivably penicillin may act not by combining with vital cellular components but by serving as an abnormal metabolite incorporated into these components This concept fails to account for similar reactivity with penicillin of actively multiplying cells of resting cells and of cell extracts

[These observations do not seem to provide a complete answer but they serve to illustrate some of the current thinking and approaches being employed by one of the outstanding contributors to our knowledge of the mechanism of antibiotic action —Ed]

Importance of Laboratory in Antibiotic Therapy S Stanley Schneierson and Morton S Bryer[2] state that the laboratory has become an indispensible adjunct to the rational use of antibiotics in infectious diseases and can prove of inestimable value to the clinician in many ways Discovery of the causative agents of disease and determination of their sensitivity to any

(2) J Mount Si H p 20 155 164 S pt Oct 1953

available antibiotic singly or in combination are two important laboratory contributions

It must be realized that time is needed to isolate and identify organisms and to perform sensitivity tests Nothing can be done to expedite the cultivation of organisms since the inherent time required for the growth of each strain is a biologic function beyond technical control An extremely valuable simple and rapid procedure which is all too often omitted is the preparation of smears from pathologic material Examination of these stained or unstained smears often supplies sufficient information for a satisfactory tentative diagnosis An effective therapeutic regimen can often be based on this

Sensitivity tests may be of little consequence when such universally sensitive organisms as pneumococcus meningococcus or gonococcus are concerned However when hardier species such as Escherichia coli staphylococcus Streptococcus faecalis proteus or Pseudomonas aeruginosa are present the assays may prove all important It has been shown that a greater proportion of strains of E coli proteus Staphylococcus aureus and albus and Str faecalis are now resistant to aureomycin and of E coli proteus and Ps aeruginosa to chloramphenicol than when the drugs were first introduced clinically Moreover in many groups there is great variation in the individual sensitivity to any given antibiotic so that generalizations with respect to a given species are no longer tenable

Clinical results do not always parallel in vitro findings Many intrinsic factors in the body not measurable by laboratory methods greatly influence clinical results The concentrations of antibiotic at the site of infection the number of infecting organisms at this focus and the nature of the lesion with its effect on the extent and degree of inflammatory reaction are all important The organisms may be deep seated and surrounded by fibrous and granulation tissue and may thus be protected from the action of the antibiotic The immune response of the host to the bacterial infection is another important determinant Despite these factors none of which is measured during the performance of sensitivity tests a surprising degree of correlation is found between the in vitro assays and the clinical response in a significant percentage of

cases Thus the finding of a strongly resistant etiologic agent in the laboratory almost always precludes the chances of achieving a gratifying therapeutic result If the causative organisms have been found to be sensitive in vitro success is more likely

There are many valid reasons for administering more than one antibiotic at a time The infection may be due to a mixture of organisms each in turn being sensitive to different drugs The most compelling indication for using such combinations is the fact that clinical experience has shown that in certain diseases a higher percentage of cures is obtained by administration of two or more drugs than when either is used alone even in higher doses The test tube readily lends itself to the determination of the sensitivity of any organism to a combination of any number of antibiotics However a drawback to this method is that it requires materials and skills only available in large laboratories Simpler technics such as the disk method may be more feasible

Progress after treatment or the lack thereof can best be measured with the assistance of the laboratory Persistence of the infecting organisms even though the infection has apparently subsided clinically denotes a lack of a completely satisfactory response and usually calls for a change of therapeutic tactics

[Sad but true the introduction of many clinically useful antibiotics has only served to render laboratory control more essential than before The constant shifting in relative sensitivity of various pathogenic microorganisms makes impossible the establishment of reliable guides based on past clinical experience instead we must depend on a good laboratory for guidance in each case Fortunately some important pathogens are uniformly and unchangingly sensitive to penicillin (pneumococcus gonococcus beta hemolytic streptococcus) But for infection due to the coliform bacilli proteus staphylococci and alpha streptococci we must nearly always depend on the laboratory for help Perhaps the most urgent present need is for laboratory methods to help the clinician assess the possibility of synergistic action by two or more antibiotics The practical difficulties in this kind of work are discussed in the subsequent article by an eminent British bacteriologist.—Ed]

Combined Chemotherapy in Bacterial Infections has become so common that its merits demand examination according to L. P Garrod[3] (Univ of London) Among indications for combined therapy are the urgent undiagnosed case mixed and double infections and the prevention of toxic effects Fre

(3) Brit. M J 1 953 957 M y 2 1953

mature and blindly directed treatment may however obscure the diagnosis and should not be begun until specimens have been obtained for study The three listed indications for the use of combined therapy are of much less significance than the prevention of acquired resistance and the achievement of synergism Acquired bacterial resistance is a change which threatens ultimately to extinguish the usefulness of all the available major antibiotics except penicillin

Prevention of bacterial resistance depends on more discriminate and restricted use and on combining with the main drug another with an adjuvant effect More must be learned about the mode of action of antibiotics In general terms the mechanism is almost certainly this Sulfonamides act by blocking a stage in an essential synthesis and antibiotics probably act similarly The acquisition of resistance results from a circumvention of this chemical process and substitution of another having the same ultimate effect with which the antibiotics cannot interfere If the second drug used blocks this second process the alternative metabolic route cannot be established and the organism therefore remains sensitive

Another advantage of combined therapy can be (but by no means always is) the achievement of a synergic effect When Streptococcus faecalis is exposed to an optimal concentration of penicillin the initial bactericidal effect is incomplete and is followed eventually by growth if on the other hand streptomycin is added even in a concentration which would be ineffective if used alone the initial rate of killing is accelerated and continues to a point of total sterilization Four penicillin resistant cases of Str faecalis endocarditis were highly sensitive to chlortetracycline yet treatment with this drug for six weeks proved ineffective Like chloramphenicol it failed but the infection was controlled in all four patients by penicillin and streptomycin

In relation to the task which chemotherapy has to perform bacterial endocarditis is an exceptional perhaps unique disease It is not enough as in most other infections to prevent further bacterial growth and leave the disposal of survivors to the body defenses in this disease those defenses are powerless Chemotherapy must eliminate the last surviving streptococcus in the vegetations if relapse is not to occur That a bactericidal drug (penicillin) should be necessary or

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(3) Brit. M J 1 953-957 May 2 1953

that in the United States during 1951 324 tons of penicillin were produced (2 000 000 units for every person in the country) This is enough penicillin to cure each person of one attack of pneumococcic pneumonia During the same year 167 tons of streptomycin were produced enough to treat 1 000 000 persons with pulmonary tuberculosis for an entire year or to manage all the new cases that developed during the past 10 years

Although chloramphenicol chlortetracycline and oxytetracycline have been in commercial production for only two or three years 250 tons of these were produced in 1951 a quantity sufficient to provide for approximately 200 000 000 patient days of treatment These figures are even more impressive when it is realized that more than half of all prescriptions written during 1951 were for antibiotics Americans spent one third of their entire drug bill during that year for antibiotics

Many persons are receiving antibiotics without accepted indications for their use and without apparent benefit Some of these patients have adverse reactions and many others may be affected by the changing bacterial patterns or by hypersensitivity reactions on later administrations of the drug The hazards of antibiotic administration are sufficient to require restriction of their use to those illnesses for which they have an appreciable effect Reactions can be greatly minimized by the following rules of therapy (1) Make an accurate clinical and etiologic diagnosis before treatment whenever possible (2) Treat the patient s illness specifically (*a*) in the selection of the antibiotic using a single agent when it is effective (*b*) in the choice of the dose and route of administration and (*c*) in the duration of treatment (3) Limit the use and time of therapeutic trials (4) Be familiar with the course of the disease to be expected under antibiotic therapy (5) Know the adverse consequences of treatment common to each of the agents (6) Observe patients during treatment for early signs of sensitivity toxicity or superinfections and weigh the possible risks before continuing treatment

[These facts and simple rules are worth a little scrutiny We would achieve a significant reduction in the harmful side effects of antibiotics (and in the size of the nation s drug bill) by following one sound policy antibiotics should not be given in treatment of the common cold —Ed]

Fatal Fungus Infections Complicating Antibiotic Therapy in three cases are reported by Curtland Brown Jr Simon

in this particular infection a highly bactericidal combination is not surprising There are few reports of cures of this disease by any of the newer antibiotics

Repeated viable counts in various mixtures and the plotting of death curves constitute a tremendous project in any laboratory A simpler method of evaluating combined effects must therefore be found if laboratories are to provide guidance for such treatment For testing four antibiotics singly and in every possible combination only 10 tubes of broth are required provided only a single combination of each antibiotic is to be tested The difficulty with such a simplified method is to choose appropriate single concentrations of antibiotics since to vary them would immediately complicate the procedure even two concentrations instead of one would involve 36 tubes instead of 10

Although interference by sulfonamides with the action of penicillin is only apparent interference by other antibiotics due to a similar mechanism is not merely demonstrable in vitro but verifiable by therapeutic tests Clinical evidence of antagonism has been demonstrated in meningococcic meningitis in which fever and mental abnormality were prolonged by the combination of chlortetracycline with penicillin Several authors feel that conditions in the meninges are ideal for antagonism as critical concentrations for this effect are fairly constant in an area where efficient bactericidal action is probably imperative Whether or not antagonism occurs in other situations future clinical observation must decide

No general rules about synergism and antagonism can be laid down The same pair of antibiotics may exhibit either effect against different organisms according to their degrees of sensitivity In any serious case the simplified bactericidal test may afford useful indications with little delay and provide a rational basis for treatment The actions of chemicals whether simple germicides or chemotherapeutic agents on bacteria can be evaluated in the laboratory to provide a reliable guide to their use Garrod adheres to this view but has begun to doubt whether such evaluations of combined antibacterial action are practicable

Adverse Effects of Antibiotic Treatment George Gee Jackson and Harry F Dowling[4] (Univ of Illinois) report

(4) GP 8 34 40 A gu t 1953

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Propp C Maynard Guest Richard T Beebe and Lawrence Early[5] (Albany Med College) Candida albicans has long been known to cause local infection in the mouth skin nails and vagina In the past such lesions have shown little tendency to spread and have rarely been fatal Recently however there has been a notable increase in the incidence of generalized and fatal infections caused by fungi particularly C albicans The danger of increased virulence of C albicans during antibiotic therapy is therefore emphasized

Man 50 was hospitalized on complaint primarily of chills and fever For several months he had been coughing and a week before he felt abdominal pain then began to have high fever In the past 10 days he had received oxytetracycline for 4 days then chloram phenicol for 3 Chlortetracycline (1 day) and penicillin therapy (2 days) followed He had signs of pulmonary infiltration and had ab dominal pain and an intravenous pyelogram disclosed a defect in the right kidney shadow The urine contained yeast cells and C albi cans was grown from blood cultures Sputum and urine specimens yielded C albicans He died on the 10th hospital day after a down hill course despite antibiotic and iodide therapy

Autopsy disclosed a right perinephric abscess adjacent to a perforation of the duodenum in which a toothpick was found There were thrombosis of the inferior vena cava and multiple pulmonary emboli Histologic study disclosed yeast cells in the thrombus and throughout both lungs Candida albicans was cultured from the peri nephric abscess

In each of the three cases C albicans was identified More than one antibiotic had been used in each case reported in the literature in these three and in two other patients who had monilial absces es in the myocardium kidneys and lungs In one of these blood cultures grew C albicans and in the other C tropicalis

[We have seen several instances of this at our hospital There can be no reasonable doubt that systemic monilial infections are much more common than previously and that they are induced in some way by anti biotic therapy —Ed]

Clinical Trials

Use of Antibiotics in Nonbacterial Respiratory Infections Philip N Jones Roy S Bigham Jr and Phil R Manning[6] (U S Air Force) call attention to the common use of anti biotics in nonbacterial respiratory infections despite lack of proof of their specific value in these syndromes Antibiotics are given with the hope of preventing secondary bacterial in

(5) J A M A 15 206-207 M y 16 1953
(6) Ib d. 153 6 64 S pt. 26 1953

fection The authors investigated their value as prophylaxis against complications in the nonbacterial influenza like syndrome

All patients with respiratory disease were admitted from the dispensary to open respiratory wards In strict order of admission to the ward and before examination by the physician each patient was placed on one of three treatment schedules acetylsalicylic acid 600 mg every six hours erythromycin 200 mg every six hours and oxytetracycline 500 mg every six hours The supply of erythromycin was exhausted during the study and in the later phases new patients were alternated between the acetylsalicylic acid and oxytetracycline schedules

Some or all of the following complaints were present on admissions headache lumbar backache general muscular aches fever nonproductive cough mild sore throat and nasal congestion All patients were admitted within 12 18 hours after onset of symptoms Those whose throat cultures showed hemolytic streptococci were excluded and a maximal initial leukocyte count of 8 500/cc was established for inclusion in the group After all patients were eliminated who failed to meet the arbitrary criteria as established for this influenza like syndrome the records of 150 were left for examination Of the e 76 (50 7% of total) received oxytetracycline and became afebrile in an average of 41 hours Fifty four (36%) given acetylsalicylic acid became afebrile in an average of 30 hours whereas the remaining 29 (13 3%) on erythromycin required an average of 42 hours

Neither oxytetracycline nor erythromycin altered the course of the disease Patients given acetylsalicylic acid usually felt better sooner than those receiving either of the other drugs

No secondary bacterial infection was observed in this series in either the patients treated with antibiotics or the patients treated with acetylsalicylic acid Thus it appears that administration of antibiotics routinely to prevent secondary bacterial involvement is not justified statistically If secondary infection develops the appropriate antibiotic should be used

[Add to the list of acute febrile disorders in which antibiotics are not of value grippelike respiratory illness without sore throat or pneumonia.—Ed.]

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(6) Ib d 153 6 204 Sept 6 1953

tetracycline chloramphenicol dihydrostreptomycin penicillin polymyxin B and neomycin in various dilutions ranging from 100 µg to 0 048 µg /ml The same micro organisms were similarly tested against all possible combinations of these antibiotics with each other and with gantrisin* and a triple sulfonamide preparation Results revealed that against all of the bacterial strains commonly cultured in urinary tract infections some combination of these antibiotics was more effective than a single antibiotic although these differences were not

TABLE 2 —In Vitro Effectiveness of Combinations of Antibiotics

	% S a ins C mpl te y I h it b 0 5 µg /ml
E coli	
Streptomycin plus chlortetracycline	85
Chlortetracycline plus chloramphenicol	85
Chlortetracycline plus polymyxin B	79
Streptomycin plus oxytetracycline	62
Str faecalis	
Streptomycin plus chlortetracycline	83
Chlortetracycline plus chloramphenicol	72
Chlortetracycline plus polymyxin B	65
Streptomycin plus oxytetracycline	64
A aerogenes	
Streptomycin plus chlortetracycline	86
Polymyxin B plus chlortetracycline	86
Chloramphenicol plus chlortetracycline; Neomycin plus chlortetracycline; Chloramphenicol plus oxytetracycline	71

T t l ot t f ntbot w md up f y l p f a h tb t

always of great magnitude These findings are in agreement with the authors clinical experience The combinations given in Table 2 were more effective against Escherichia coli Streptococcus faecalis and Aerobacter aerogenes

Clinical trials with the various combinations are too incomplete for any conclusions but they do show that rational combinations of antibiotics and of antibiotics with sulfonamides give more bacteriologic cures (as demonstrated by negative cultures on catheterized urine made at least 48 hours after cessation of 5 7 days of therapy) than any agent used alone

Efficacy and Toxicity of Oxytetracycline (Terramycin®) and Chlortetracycline (Aureomycin) With Special Reference to Use of Doses of 250 Mg Every Four to Six Hours and to Occurrence of Staphylococcic Diarrhea After its introduction in 1948 chlortetracycline was rapidly recognized as

Study of in Vitro Activity of Antibiotics and Sulfonamides, Singly and in Combinations, against Micro organisms of Urinary Tract Paul S Rhoads Carl E Billings and Doris M Adair[7] (Chicago) state that their studies of urinary tract infections have revealed that if one adheres to rigid criteria for actual control of the infection results of therapy are apt to be disappointing With full doses of appropriate antibiotics or sulfonamides (Table 1) it was relatively easy to alleviate the symptoms of most acute attacks of cystitis or pyelonephritis and render the urine free from pus However when cultures of catheterized urine were made at least 48 hours

TABLE 1—DOSAGE SCHEDULE FOR VARIOUS URINARY ANTISEPTICS

Chlortetracycline, Chloramphenicol, Oxytetracycline } First dose 1 0 Gm then 0 5 Gm every 6 hr (day and night)
Dihydrostreptomycin First dose 1 0 Gm then 0 5 Gm every 6 hr (day and night)
Penicillin 400 000 units of crystalline and procaine preparation (or straight crystalline) every 12 hr
Polymyxin B 0 05 Gm intramuscularly every 6 hr
Mandelamine 0 25 Gm (3 tablets) every 6 hr
Calcium mandelate 3 0 Gm every 6 hr
Gantrisin ® 1 5 Gm every 6 hr
Triple sulfonamide 1 5 Gm every 6 hr

after 5 10 days of what was considered adequate therapy the majority were positive either for the micro organisms found in pretreatment cultures or for one or more new strains For permanent cure of urinary tract infections all lesions obstructing the free flow of urine in either the upper or the lower portions of the urinary tract such as ureteral or urethral strictures or calculi prostatic obstruction cystocele and tumors had to be removed Vaginitis chronic enteritis colitis and other infections spreading to the urinary tract directly or via the blood or lymphatic routes usually had to be cleared up also

In many instances use of two antibiotics simultaneously or of an antibiotic with a sulfonamide gave better results than use of a single agent A study was therefore undertaken in the hope of discovering the most useful combination of antibacterial agents to use in stubborn infections In vitro tests were made on 156 micro organisms obtained in cultures of *catheterized urine* for sensitivity to chlortetracycline oxy

(7) A t b t & Ch m th 3 721 730 J ly 1953

tetracycline chloramphenicol dihydrostreptomycin penicillin polymyxin B and neomycin in various dilutions ranging from 100 µg to 0 048 µg /ml The same micro organisms were similarly tested against all possible combinations of these antibiotics with each other and with gantrisin® and a triple sulfonamide preparation Results revealed that against all of the bacterial strains commonly cultured in urinary tract infections some combination of these antibiotics was more effective than a single antibiotic although these differences were not

TABLE 2—IN VITRO EFFECTIVENESS OF COMBINATIONS OF ANTIBIOTICS*

	% Strains Completely Inhibited by 0 5 µg/ml
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Streptomycin plus oxytetracycline	64
A aerogenes	
Streptomycin plus chlortetracycline	86
Polymyxin B plus chlortetracycline	86
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* Total content of antibiotic [illegible]

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an important and highly effective agent against many infectious diseases Oxytetracycline, introduced two years later was soon found to have almost identical activity Both antibiotics now rank among the most important antimicrobial agents available

During clinical evaluation of oxytetracycline a large number of patients had diarrhea with or without upper gastrointestinal symptoms in many hemolytic coagulase positive strains of Staphylococcus aureus were found in pure culture or as the predominant organisms in watery feces Some of the staphylococcic diarrheas were severe and may have caused or contributed to the death of a few patients

Later it was noted that untoward gastrointestinal effects were less frequent and less severe when smaller individual doses of the drug were used Moreover clinical and bacteriologic results in patients receiving the smaller doses did not appear to be appreciably different from those in patients treated with larger doses Accordingly a special study was instituted by Maxwell Finland Margaret E Grigsby and Thomas H Haight[8] (Harvard Med School) in an attempt to determine the over all efficacy and toxicity of oxytetracycline in doses of 250 mg every four to six hours A parallel study was also undertaken with chlortetracycline for comparison Altogether 520 patients were given either oxytetracycline or chlortetracycline chiefly for infections of respiratory or urinary tracts Most patients were given 250 mg orally every four or six hours 37 patients received 500 mg at similar intervals

Results with the two antibiotics were fairly comparable considering the relatively small number but wide variety of cases treated and the number and character of the underlying complicating factors No conclusions could be drawn with respect to the relative efficacy of dosage regimens used compared with larger dosages used previously

The most frequent toxic effects were on the gastrointestinal tract The frequency of gastrointestinal complications particularly severe diarrhea was significantly greater in patients given oxytetracycline than in those who received chlortetracycline in the same dosage With each diarrhea was about twice as frequent among patients who received 250 mg every

(8) A M A Arch Int M d. 93 23 43 Jan y 1954

four hours or 500 mg every four of six hours as among those given 250 mg every six hours

Diarrhea subsided rapidly and normal flora returned in the stools in most cases when oral administration of the of fending antibiotic was discontinued and only general suppor tive measures were instituted

[The fact is that we are having fewer toxic effects now than formerly and the principal reason seems to be a tendency to hold the total dose to no more than 1 0 gram daily These studies appear to show that chlortetracycline is less likely to cause gastrointestinal disturbance than oxytetracycline If present indications are borne out by larger experience tetracycline may be even better (See next article)—Ed]

Clinical and Laboratory Observations of a New Antibiotic, Tetracycline, are described by Maxwell Finland Elmer M Purcell Samuel S Wright Ben Del Love Jr Thomas W Mou and Edward H Kass[9] (Harvard Med School) Simul taneous tests for sensitivity to tetracycline oxytetracycline and chlortetracycline made with 257 recently isolated strains of common pathogenic bacteria revealed that organisms highly resistant to one of the agents were always resistant in about the same degree to the other two In a test to determine peak levels 12 volunteers received single oral doses of 1 Gm of each of the three tetracyclines by mouth in rotation at dif ferent times With all three agents peak levels were achieved between four and six hours and generally ranged from 1 to 4 μg/ml plasma

A clinical trial was carried out in 118 patients treated with tetracycline hydrochloride given in tablets or capsules orally by intravenous injection or by both routes About half re ceived 500 mg orally every six hours the rest received 200 or 250 mg every four or six hours An initial oral dose of 1 Gm was given to a number of patients on each of the regi mens and some who received individual doses of 200 or 250 mg were given 500 mg initially Intravenous doses of tetra cycline hydrochloride were given in 0 5 to 1 0 Gm amounts dissolved in 1 1 5 L isotonic sodium chloride solution by slow infusion at intervals of 12 hours or longer This was the only therapy used in five patients but it was used during the first day or two in 13 other patients before oral dosage was started

Therapeutic results with tetracycline in this study were similar in every respect to those obtained in a controlled

(9) J.A M A 154 561 568 F b 13 1954

clinical study of the effects of oxytetracycline and chlortetracycline The most striking and encouraging feature was the relatively low frequency of toxic effects in contrast to previous experience with chlortetracycline and especially oxytetracycline All of the untoward effects observed from tetracycline in the present study were limited to gastrointestinal symptoms but these were distinctly less frequent and less severe than those noted in the study with oxytetracycline and chlortetracycline

In the present study five patients given tetracycline orally had mild and brief diarrhea One patient had diarrhea for two days Only one had a large number of staphylococci (mixed with a large number of enterococci) in the feces

Erythromycin for Infections Due to Micrococcus Pyogenes One of the most important problems in the therapy of infectious diseases is the management of infections due to strains of Micrococcus pyogenes (Staphylococcus aureus) which are resistant to many antibiotics Wallace E Herrell Donald R Nichols and William J Martin[1] (Mayo Clinic) report their experience with erythromycin in 54 patients with M pyogenes infections 8 of whom had septicemia The organisms were relatively insensitive to penicillin streptomycin chlortetracycline and oxytetracycline in most instances

In six of the cases of septicemia erythromycin proved life saving Bacterial resistance to erythromycin has been demonstrated in vitro but it developed slowly In the two cases in which failure occurred the organisms became resistant in vivo with extreme rapidity the rapid reversal being similar to that seen with streptomycin For this reason and because bactericidal serum levels of erythromycin are not easily attained with the doses generally used it is recommended that erythromycin not be used routinely in treating bacterial endocarditis due to M pyogenes

Of 17 cases of skeletal and soft tissue infections due to M pyogenes a satisfactory or excellent clinical result was obtained in 8 Though a few of the nine failures were due to development of erythromycin resistance it may be that in some instances adequate amounts of drug could not reach the infected areas

Fourteen patients with staphylococcic ileocolitis given

(1) J A M A 152 1601 1606 Aug 2 1953

erythromycin orally recovered completely This condition may be severe but is rarely fatal and its management is relatively simple If a patient i receiving broad spectrum antibiotics when ileocolitis develops their administration is discontinued immediately and the patient given erythromycin orally Within 24 72 hours clinical improvement is evident and the normal flora is found once again on stool culture

Erythromycin was successful in eliminating M pyogenes from the stools of five patients who harbored the organism but had no symptoms of infection In the one case of meningitis due to a strain of M pyogenes relatively resistant to penicillin and the broad spectrum antibiotics the infection responded to erythromycin Urinary tract infections acute infections of the nose or throat and postoperative empyema responded well to erythromycin

The oral dose for an average adult is 300 400 mg every six hours Doses larger than 400 mg may cause gastrointestinal irritation Preparations are available for intravenous administration and should be given only to persons who cannot take the medication orally The average adult dose for intravenous administration is 250 mg dissolved in buffer solution given every six or eight hours No serious toxic reactions have been encountered after the use of erythromycin in the amounts used in this series

[This drug certainly ha an important place in management of acute staphylococcic infections (except staphylococcic endocarditis) Because the development of resistance to it is usually delayed by combination therapy it probably should always be administered in conjunction with another antibiotic such as penic llin streptomycin bac tracin or chloramphenicol Laboratory tests may help in selection of the proper c mbination —Ed]

Treatment of Staphylococcic Infections with Erythromycin From the standpoint of antibiotic therapy infections caused by staphylococci constitute one of the major problems In hospitalized patients about 70% of these infections are caused by penicillin resistant and 40 60% by chlortetracycline and oxytetracycline resistant organisms William M M Kirby Trygve Forland and Francis M Maple (Seattle) report results of erythromycin therapy in 34 patients with infections caused by antibiotic resistant staphylococci Before therapy all strains were highly sensitive to erythromycin and resistant to chlortetracycline oxytetracycline and penicillin Erythro

( ) A M A A h I t M d 9 464-470 O t b 1953

mycin was administered in tablet form in doses of 0 3 or 0 5 Gm every six hours Therapy was usually continued for 7 14 days but in a few cases as long as 2 months There were virtually no side reactions and the tablets were well tolerated The patients were generally only moderately ill and none was bacteremic Evaluation of results in 22 patients with soft tissue infection was complicated by the fact that in many instances abscesses were drained and wounds opened widely However there appeared to be improvement attributable to the antibiotic therapy

Of 10 patients with osteomyelitis only 1 seemed unim proved Though other therapeutic measures were carried out results of erythromycin treatment were impressive and seemed comparable to those which would have been obtained with penicillin had the organisms been sensitive to this antibiotic

The favorable results in the entire series are not surpris ing in view of the marked sensitivity of staphylococci to erythromycin in vitro and the relatively high blood levels which are easily attainable with this antibiotic However it has been observed recently chiefly in staphylococcic endo carditis that the infecting organisms rapidly become resistant to erythromycin Development of erythromycin resistant staphylococci was observed only once in the present series in a patient with osteomyelitis of the spine treated for six weeks

Relative Efficacy of Erythromycin (Ilotycin) and of Penicillin in Treatment of Pneumococcic Lobar Pneumonia was studied by Robert Austrian Robert Rosenblum and the Pneu monia Study Group[3] (State Univ of New York Brooklyn) The antibacterial spectrum of these two antibiotics is similar

Patients treated with erythromycin received 400 mg on hos pitalization and 400 mg every six hours thereafter Treatment was continued until rectal temperature was below 99 6 F for 72 hours Patients receiving penicillin were given 300 000 units of the aqueous sodium salt intramuscularly on admission and every 12 hours thereafter until rectal temperature was below 99 6 F for 72 hours

Of the 50 patients studied 24 were given erythromycin and 26 penicillin The infections were considered of comparable severity except for the higher incidence of bacteremia among

(3) Am J M Sc. 226 487 490 November 1953

patients treated with erythromycin Two of the erythromycin treated group died A man 82 with bacteremia due to pneu mococcus type II died suddenly four hours after his initial and only dose of erythromycin The other death occurred in a diabetic man 63 in shock who had bacteremia due to pneu mococcus type III The one death in the penicillin treated group was that of a man 78 with uremia and bacteremia due to pneumococcus type III He died 9 days after hospitaliza tion and autopsy 14 days after death revealed multiple small abscesses in the left lower lobe

Within two days after the start of therapy 13 (54 2%) of the erythromycin treated patients and 12 (46 5%) of the penicillin treated group had temperatures below 99 6 F rec tally Two days later the temperatures of the other patients on each drug were below 99 6 F rectally White blood cell counts fell below 10 000/cu mm within six days in 12 (50%) patients receiving erythromycin and in 17 (65%) of those given penicillin Four patients receiving erythromycin and six given penicillin had counts above 10 000/cu mm for seven days or more

In each group two patients had clinical and roentgen evi dence of pleural effusion which resolved spontaneously Reso lution of the pneumonic process was delayed longer than three weeks in one patient in each treatment group No untoward reactions could be ascribed with certainty to either drug however one possible instance of drug fever followed admin istration of erythromycin

Results of this study suggest that erythromycin is a suit able drug for treatment of pneumococcic lobar pneumonia It exerts antibacterial activity against a limited number of bac terial species and therefore should be used only when labora tory facilities permit an etiologic diagnosis to be established Furthermore some bacterial species including pneumococcus may develop in vitro a clinically significant degree of resist ance to erythromycin Although clinical failure in the treat ment of pneumococcic pneumonia with erythromycin as a result of this phenomenon has not yet been reported the pos sibility of such an event makes the antibiotic a potentially less satisfactory drug than penicillin Finally the relative insolu bility of erythromycin and the unavailability of a preparation for parenteral administration at the time of study have made

it seem less suitable for treating critically ill patients who might require immediate establishment of adequate blood and tissue levels of an antibacterial agent For these reasons it is suggested that erythromycin be reserved as an alternative form of therapy for pneumococcic lobar pneumonia its value being that it may be administered to patients sensitized previously to penicillin

Neomycin Lotion in Treatment of Cutaneous Bacterial Infections is discussed by M Allen Forbes Jr[4] (Univ of Texas) Neomycin is not used systemically because of its ototoxic and nephrotoxic effects Therefore possible sensitization to the antibiotic after topical treatment does not deprive the patient of a valuable therapeutic agent for treatment of a subsequent systemic infection

In certain patients there is a distinct advantage in using a lotion rather than wet dressing or an ointment Neomycin is the only broad spectrum antibiotic available which is stable in an aqueous solution for an indefinite period

Of 126 patients with cutaneous bacterial infections—impetigo impetiginized eczematous dermatitis otitis externa folliculitis ecthyma and bacterial paronychia—109 responded *satisfactorily to aqueous neomycin solution in seven days or* less Before treatment hemolytic staphylococci were cultured from approximately 81% of these cutaneous bacterial infections and beta hemolytic streptococci from 6% From the other infections nonhemolytic staphylococci proteus pseudomonas and Sarcina lutea were isolated

The patients with impetigo folliculitis and ecthyma responded more rapidly than those with impetiginized eczematous dermatitis and otitis externa The patients with impetiginized eczematous dermatitis consisted of those with an underlying condition such as seborrheic dermatitis atopic eczema or secondarily infected tinea pedis No instances of sensitization or primary irritation were seen

[The author prepared a lotion with a fairly complicated formula Doubtless commercial preparations will be available for general use —Ed]

Problems in Treatment of Refractory Bacterial Infections Morton S Bryer and S Stanley Schneierson[5] discuss the refractoriness of such organisms as proteus Pseudomonas aeruginosa the coli *aerogenes group* Staphylococcus *aureus*

(4) A M A A h D rmat & Syph 68 631 634 De emb 1953
(5) J Mt S n Ho p 0 85 29 J F b 1954

and the enterococcus to the antibiotics in common use Proteus may be inhibited by neomycin Ps aeruginosa by polymyxin the coli aeruginosa group by polymyxin or neomycin Staph aureus by erythromycin or magnamycin® and the enterococcus by combination of streptomycin penicillin and bacitracin or the broad spectrum antibiotics Rigidly standardized and controlled laboratory sensitivity tests are essential to determine the antibiotic most appropriate for treatment of all refractory infections

Polymyxin B available in 50 mg vials is given intramuscularly four to six times a day individual doses never exceed mg 1 mg/kg It is poorly absorbed from the gastrointestinal tract and does not pass readily from the blood into the cerebrospinal fluid Neomycin which may damage the eighth nerve or the kidneys is given in four equal intramuscular doses daily to a total daily dose of 10 mg/kg Maintenance of a daily urinary output in excess of 500 cc is important Bacitracin which may also cause renal damage is administered in a daily dose of 1 000 units/kg in four intramuscular injections It does not pass into the cerebrospinal fluid Since neomycin polymyxin B and bacitracin are irritating locally they should be injected with 1 2% procaine Erythromycin magnamycin® and furadantin® are newer antibiotic and chemotherapeutic agents which may help to combat organisms resistant to the more widely used antibiotics Polymyxin neomycin and bacitracin are more toxic than the older antibiotics and should therefore be used with proper precautions

[This is useful reference material on the ind cations dosage and toxicity of the less commonly used ant biotics —Ed]

Carbomycin Therapy Results of Brief Clinical Trial, Chiefly in Patients with Pneumonia are reported by Maxwell Finland Elmer M Purcell Samuel S Wright and Ben Del Love Jr [6] (Harvard Med School) This antibiotic is derived from a culture of Streptomyces halstedii In addition to 40 patients with pneumonia 5 with miscellaneous infections were treated

The pneumonia was judged to be mild or moderate in all but two patients and seven had blood cultures positive for pneumococci All but 2 of the 40 pneumonia patients were given the antibiotic orally Oral therapy was initiated with a

(6) N w E gl nd J M d 49 310 318 Aug 0 1953

dose of 500 mg usually followed by 2 or 3 Gm daily given as 250 mg every three hours or 500 mg every four hours The other two patients were treated intramuscularly

Clinically the acute pneumonic symptoms persisted five days or longer in 15 patients Nine required more than two full weeks of hospitalization for the pneumonia or its complications Of the seven patients with positive blood cultures before carbomycin therapy five continued to have positive cultures for periods up to six days or until penicillin was substituted Continuance of carbomycin therapy was believed not justified in 12 patients and penicillin was substituted

About half the patients were considered to have shown a favorable response to carbomycin Only six had a response comparable with that observed in similar patients treated with penicillin chlortetracycline oxytetracycline or erythromycin

Of the five patients with miscellaneous infections only one with acute tonsillitis, possibly benefited from carbomycin therapy

Gastrointestinal symptoms were noted in 11 of the 43 patients given carbomycin orally Nausea and vomiting occurred in five diarrhea without vomiting in four and nausea vomiting and diarrhea with abdominal cramps in two

The clinical and bacteriologic results of carbomycin therapy in the patients with pneumonia indicate that this antibiotic is not highly effective in such cases even when used in doses approaching the maximum tolerated by most patients

On the basis of the results in these cases and in those thus far reported carbomycin cannot be recommended as a useful antibiotic in bacterial infections and is considered to be specifically contraindicated in pneumococcic infections

[Carbomycin—farewell!—Ed]

Use of Chloromycetin® in Treatment of Salmonella Carriers in a State Institution Ivan A LaCore and John H Conlin[7] point out that salmonella infections have always been a problem in state institutions At Ypsilanti (Mich) State Hospital it has been routine for some time to make bacteriologic analysis of stool samples of each patient on admission In August 1952 the number of reports of stools positive for salmonella infections suddenly increased greatly After active infection appeared in a number of patients it was decided to treat both

(7) Am J M S 225 547 550 M y 1953

patients so affected and carriers as chronic carriers were probably the source of the active infections Previous reports on the use of chloramphenicol (chloromycetin®) were so encouraging that this antibiotic was used

Twenty five carriers were selected on the basis of consecutive admissions with positive stool cultures Twelve salmonella types were recovered and 11 were identified No typhi or paratyphi were recovered

Patients were divided into four treatment groups and all but two patients were given the medication orally Six received 50 mg /kg /24 hours for five days and only three were bacteriologically cured Eleven men were given 100 mg /kg /24 hours for seven days and of these 10 were cured Five women were treated similarly (two parenterally) and four responded satisfactorily A fourth group of six patients which included the one in the second group who did not respond were given 100 mg /kg /24 hours for seven days Five were treated successfully and the other patient responded on retreatment

The optimal dose schedule for chloramphenicol treatment of salmonella carriers appears to be 100 mg /kg /24 hours for seven days No toxic reactions were observed during or for several months after treatment

[These results are much better than those obtained with chloramphenicol in treating carriers of S typhi —Ed]

Further Trial of Aureomycin in Treatment of Cholera S C Seal M M Ghosh and S C Ghosal[8] (Calcutta) treated 50 patients with cholera with aureomycin (chlortetracycline) orally 35 with sulfaguanidine and 35 with saline Average total dose of chlortetracycline was 23 capsules (250 mg each every three hours) and of sulfaguanidine 26 Gm The three groups were similar with regard to age clinical stage specific gravity of blood condition of urine and positive isolation of Vibrio cholerae There was no difference in the fatality rates among the three groups (about 14%) In certain minor points chlortetracycline treatment showed some advantages *Average duration of suppression of urine in the group treated* with this antibiotic was significantly less than that in the other groups the acute stage was shorter the period of excretion of vibriones was reduced and the average number of stools was less There were no serious toxic effects due to chlortetracycline

(8) B t M J 1 740 74 M 27 1954

It is believed that chlortetracycline had some influence on the course of the disease The failure of any drug in the advanced stages of cholera does not necessarily mean that it has no action on the cholera vibrio Chlortetracycline is vibriocidal in vitro and the quicker disappearance of the organism from convalescent patients indicates that it is also effective in vivo The dose used was probably high A lower dose of 3 5 Gm depending on the stage of the disease may be sufficient

Chemotherapy of Experimental Plague in the Primate Host F R McCrumb Jr A Larson and K F Meyer[9] (Univ of California) studied the pathogenesis of untreated disease in rhesus monkeys and attempted to evaluate the use of modern antibiotics in control of bubonic and pneumonic plague in the host Striking similarity between human plague and that observed in certain species of monkeys has been noted

Bubonic and pneumonic plague were induced in the monkeys Overwhelming bacteremia with protracted hypotension characterized the terminal phases of the bubonic form Rapidly progressive pneumonitis with varying degrees of bacteremia was the main feature of the disease produced by intratracheal inoculation Chloramphenicol chlortetracycline and streptomycin are effective against bubonic or pneumonic infections in the monkey if therapy is instituted during the early phases of the disease They are uniformly ineffective if introduced in the late stages Moreover the response in late cases to antibiotic therapy is not improved by the addition of cortisone or hyperimmune serums Also fatal anaphylaxis accompanied the intravenous administration of concentrated rabbit globulin to severely ill monkeys The emergence of streptomycin resistant mutants of Pasteurella pestis was seen in two instances in one chloramphenicol was successful

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STAPHYLOCOCCIC INFECTIONS

Fatal Staphylococcus Enteritis Following Penicillin and Streptomycin Therapy Fatal staphylococcus enteritis following antibiotic therapy is now a familiar entity Chester W Fairlie and Ralph E Kendall[1] (Hartford Conn) report on

(9) J I fect. D 9 273 287 M y J 1953
(1) J A M.A 155 90 94 Sep 12 1953

this entity in three cases Each patient had received only penicillin and dihydrostreptomycin intramuscularly in contrast to reports in the literature in which chlortetracycline and oxytetracycline administered orally were generally the offending agents

Fever and diarrhea were the cardinal clinical features at the onset of the condition Two patients appeared strikingly well during the first few days of the illness though there was fever of 102 104 F and death occurred four days later Shock oliguria and azotemia were prominent features in the later course Diarrhea or fever began two to nine days after antibiotic administration was started and death occurred four to eight days after onset of fever or diarrhea At autopsy on each patient severe enteritis was proved to be the cause of death and abundant and pure growth of hemolytic Staph aureus was demonstrated in postmortem bowel cultures In two cured patients the clinical picture was identical to that of the patients who died Staphylococci were not cultured from the stool in these patients but each had abnormal flora in throat and stool cultures

It is essential to recognize the possibility of this complication when unexplained fever or diarrhea develops in any patient receiving antibiotics Recognition should be followed by prompt withdrawal of the antibiotics and perhaps use of an antibiotic to which most staphylococci in the area are known to be sensitive for example erythromycin Because of the fulminating character of the illness one should not wait until the results of cultures or sensitivity tests are known before instituting therapy Attention to fluid and electrolyte balance are primary therapeutic measures

Simple suppression of intestinal flora permitting overgrowth of staphylococcus or other organisms does not seem sufficient explanation of the complications Introduction of a particular strain of staphylococci or the direct stimulation of toxin production by staphylococci under antibiotic influence might be other explanations Onset of fever and diarrhea within 24 hours after the institution of antibiotics suggests a stimulatory effect by these drugs rather than an effect secondary to the suppression of normal intestinal flora Strengthening this view is the fact that all the drugs were given par

enterally and early cultures failed to show staphylococci [Note that these followed penicillin streptomycin not the broad spectrum antibiotics —Ed]

The Antibiotic Resistant Staphylococci The apparent in crease in antibiotic resistant staphylococci is being magnified by the results of studies in hospital communities According to Henry Welch[2] the incidence of antibiotic resistant staph ylococci has increased much less than has been indicated by studies made of staphylococci isolated from hospital patients

An analysis of 78 strains of Micrococcus pyogenes derived from outpatients showed a resistance rate of 12 5% and from hospitalized patients 68 4% Wherever this problem has been studied the incidence of penicillin resistant staphylococci among hospital populations has been considerably greater than among nonhospitalized persons Although 50 70% of normal subjects may be carriers of staphylococci the impor tant consideration is how many persons under hospital care and among the general population are carriers of strains re sistant to penicillin and other antibiotics Barber *et al* have stressed that penicillin resistant staphylococcic infections are nearly always the result of hospital cross infection The pre vention of both is therefore the same and depends on the hygienic and aseptic control of the hospital It is questionable whether increased rigidity of aseptic technics generally prac ticed in hospitals will significantly reduce the incidence of staphylococcic cross infection However technics which to gether with chemotherapy have proved successful in prac tically eliminating cross infections caused by the hemolytic streptococcus should be tried

The rate of spread of antibiotic resistant staphylococci in a hospital community appears to be directly related to the aver age number of people treated with each antibiotic Wherever a preponderance of one of the broad spectrum drugs has been used most patients are found to be infected with staphy lococci resistant to that antibiotic Whether or not the isola tion of new antibiotics initially active against resistant staphy lococci will be the sole answer to the problem is questionable Application of the principles of preventive medicine may be a more logical and effective approach

Resistant strains of staphylococcus may respond to eryth romycin carbomycin bacitracin and chloramphenicol how

(2) A t b t cs & Chem th 3 561 570 J n 1953

ever strains resistant to erythromycin and carbomycin are already beginning to emerge Consideration should be given to maintaining patients treated with chlortetracycline and oxytetracycline on a minimal effective therapeutic dose There would then be less likelihood of irritating the intestinal mucosa and of disturbing the normal antagonisms among organisms of the intestinal tract which may to some degree be responsible for inhibiting excessive growth of micrococci Oral drug therapy should be promptly discontinued if diarrhea occurs on or after the third day of therapy and especially if the diarrhea is staphylococcic in origin

[This all sounds so impractical The precise percentage of penicillin resistant staphylococci in or out of ho pitals is not important. The point is that the incidence of severe staphylococcic *infections* in patients ad mitted to hospitals all over the western world is increasing at an alarming rate The preventive measures suggested do not seem to me l kely to be of practical utility —Ed]

HEMOLYTIC STREPTOCOCCIC INFECTIONS

Epidemic of Acute Nephritis in groups of associated individuals has been described in a variety of circumstances It has frequently been recognized among soldiers and referred to as trench or war nephritis Fleming reported an outbreak among adult inhabitants of congested tenement buildings where cold damp environment and poor nutrition were suggested as possible contributory factors

R W Reed[3] (Dalhousie Univ) reports 22 cases of acute nephritis which occurred in a sharply localized rural area Patients were aged 2 17 Because of the relation thought to exist between acute nephritis and hemolytic streptococcic infections throat swabs were cultured From 153 throat swabs 59 strains of beta hemolytic streptococci were recovered—56 belonged to Lancefield s group A 2 to group B and 1 to group D The extremely high carrier rate of group A streptococci corre ponded with the incidence of nephritis Further break down of the group A strains into Griffith s types showed that 53 of 56 group A streptococci were type 12

Antistreptolysin O titers were estimated in 19 cases In 15 the individual titers were above the 200 units/ml generally considered to be a normal level for the age group

(3) C d M A J 68 448 455 M y 1953

The data lend weight to the generally held opinion that hemolytic streptococci are concerned in the etiology of acute nephritis

[Evidence continues to pile up in support of the hypothesis that only certain types of hemolytic streptococci cause nephritis Of the nephritogenic strains type 12 seems to be the chief offender —Ed.]

DIPHTHERIA

Persistent Diphtheritic Heart Disorders Follow up Investigation Opinions have differed as to whether acute disorders of the myocardium commonly occurring in the acute stage of diphtheria could result in chronic heart disorders It is now generally accepted that diphtheria can cause persistent heart damage, but clinical experience seems to indicate that the incidence must be fairly small Of 1 477 patients treated for diphtheria during the epidemic of 1942-46 263 had had clinical signs of heart disease or ECG changes during the acute stage Jens Hoel and Arnold Holst Berg[4] (Kristiansand Norway) studied 210 of these patients

Questionnaires were answered by 48 patients, and 162 were examined The investigations consisted of history ordinary physical examination blood pressure recordings functional tests obtained by having the patient walk or run up stairs teleoroentgenograms of the heart and ECG studies All other possible causes of heart disease were ruled out The observation period was 5 8½ years

None of the patients who underwent clinical ECG and roentgen examination had congestive heart failure One had attacks of vertigo caused by alternating heart block Seventeen had various ECG abnormalities probably of diphtheritic origin six had prolonged conduction time four had bundle branch block and six had depressions of the S T segments or changes of the T waves in the first two limb leads Two had subacute heart disease for several years and two had heart enlargement which may have been due to diphtheria

[This seems such skimpy evidence of permanent cardiac damage from diphtheria that we would still be justified in giving an excellent prognosis to the patient who has recovered and in regarding the entity of permanent diphtheritic myocardial damage as exceedingly rare —Ed]

(4) Act med. sca di av 145 393 405 1953

The Factor of Infection in Chronic Bronchitis its cause and its course are much neglected according to C H Stuart Harris Margaret Pownall Cynthia M Scothorne and Zena Franks[5] (Univ of Sheffield) This may be due in part to the feeling that the origin of such a chronic disease is degenerative rather than infective and in part to past inability to interfere specifically with the course of infection However antibiotics now allow alteration of the symptoms of chronic bronchitis and the factor of infection becomes important Its mode of action was therefore critically evaluated

Swabs taken from healthy mucosa at the level of or even below the bifurcation of the trachea by means of bronchoscope or some similar apparatus yield no organisms or only a few colonies of nasopharyngeal organisms To explain the sterility of the trachea and bronchi in health there must be a constant process of surface disinfection effected probably by the upward moving sheet of respiratory mucus which is propelled by cilia to which are added leukocytes derived by diapedesis between the epithelial cells Mechanical factors temperature and humidity modify ciliary action and the efficacy of such a process

Above the larynx the posterior nasopharynx maintains a constant state of saprophytism with a tolerance toward certain organisms of a potentially invasive character It is generally agreed that cocci of the gram negative catarrhalis family nonhemolytic and green producing streptococci diphtheroids rough species of hemophilus and noncoagulase producing staphylococci are constant dwellers in the nasopharynx Pneumococci of many types hemolytic streptococci and Bacteria friedlanderi are also found in the nasopharynx in numbers which vary greatly and apparently at random in normal persons under different circumstances Less intensive colonization with pneumonococci and Haemophilus influenzae is present in the nose which however is the special province of the Staphylococcus pyogenes

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(5) Q rt J M d 22 121 13 Ap 1 1953

Acute viral infections of the respiratory tract undoubtedly disturb both the distribution and the quantitative relationships of the bacterial flora Even if respiratory epidemics cause no general increase of bacteria carried in the nasopharynx they probably influence the normal relationship of the host to his own flora sometimes to the host s detriment Examination of the sputum or of material obtained by bronchoscopic aspiration during the various phases of ill health in chronic bronchitis does not reveal a constant flora

The authors observed 113 patients 90 of them men in Sheffield in 1948 52 with particular reference to pneumococcus and influenza viruses in the acute exacerbations experienced by patients with chronic bronchitis with or without heart failure The pneumococcus was a common inhabitant of the sputum in all phases of the disease Other potentially pathogenic species were less common but selective mediums which favor Haemophilus influenzae were not used The influenza virus infections were detected chiefly in relation to the acute exacerbations of chronic bronchitis but infection was not invariably accompanied by clinical relapse The types of pneumococci found in the sputum were spread throughout the range of the species and the distribution resembled that found in the normal nasopharynx more closely than that found in the sputa of pneumonia patients Treatment with antibiotics exerts a definite effect on the quality and quantity of the sputum in chronic bronchitis

Rous and Friedewald in discussing the relative roles of neoplastic viruses and of chemical carcinogens distinguished between an actuating cause which persists throughout the disease and one which is provocative The latter leads to or promotes the development of lesions but subsequently disappears from them No one has yet found an infective agent which could with confidence be described as an actuating cause of chronic bronchitis No one who watches the course of bronchitis in a group of cases can doubt how acute respiratory infections from the simplest cold to full blown pneumonia promote destruction of the respiratory defense and add to the damage already present in the bronchitis patient Subsequent chronic colonization of the lower respiratory tract owing perhaps to an inability to rid the bronchi of normally inhaled organisms provides a constant source of epithelial

irritation and often causes an active inflammatory reaction In chronic bronchitis there is therefore an essential failure of defense of the lower respiratory tract against invasion by nasopharyngeal organisms and the repetitive attacks of respiratory viruses may play a large part in bringing about this situation

[The authors deserve thanks for a sound study of an important disease to which far too little study has been given --Ed]

BRUCELLOSIS

Brucellosis in Man Study of Cases Due to Brucella Abortus Wendell H Hall[6] (Univ of Minnesota) summarizes the experiences of 35 hospitalized patients in whom brucellosis was proved by culture to be caused by Br abortus All had multiple and varied complaints the predominant ones being weakness sweats and general malaise Clearcut symptoms relating to a specific system were lacking

Despite multiple symptoms few physical abnormalities were present Fever was present at some time in all the patients but varied in degree and pattern Lymphadenopathy was present in most and there was palpable enlargement of the spleen in nearly half and of the liver in one third of the patients Weight loss was seldom apparent although half the patients lost weight

The diagnosis rests principally on the epidemiologic and clinical history the agglutination test and the blood culture Only the last is decisive Bedside examination of the patient alone never permits an unqualified diagnosis The idea that an undulating recurrent fever is the rule is not true such a febrile course was present in only one fourth of the cases

A positive venous blood culture was obtained in all 35 patients Each had serum agglutinins for Br abortus in a titer of 1 160 or over No anemia was present and the initial leukocyte count was seldom elevated It was 10 000/cc or more in only two patients (maximum 11 500 median 6 000 minimum 2 500)

Chlortetracycline has proved the best therapeutic agent for human brucellosis and has been effective in suppressing symp

(6) Minnesota Med 36 4 0 465 May 1953

toms fever and bacteremia although some patients required more than one course before they recovered Chlortetracycline plus streptomycin proved no better than chlortetracycline alone Seven patients given corticotropin had almost complete subsidence of fever and symptoms despite continued bacteremia as long as corticotropin was given Fever usually recurred as soon as the hormone was discontinued and no untoward effects were observed Two recoveries were observed after corticotropin alone these may have been spontaneous Final control of human brucellosis rests on pasteurization of dairy products and elimination of the animal reservoir

Brucellar Bursitis A cursory review of the literature shows the generalized form of brucellosis to predominate

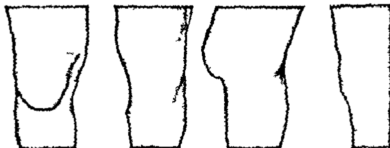


Fig 1—Enlargement of right prepatellar bursa (Courtesy of Johnson E W Jr and Weed L A J Bone & Joint Surg 36-A 133-139 January 1954)

However as brucellosis becomes more prevalent localized forms of the disease will be more evident E Wesley Johnson Jr and Lyle A Weed[7] (Mayo Clinic) report four cases of brucellar bursitis

CASE 1—Farmer 63 had swelling of the right knee for five to six years Later the knee became hot Examination revealed hydrops of the prepatellar bursa (Fig 1)

CASE 2—Farmer 60 had a swelling over the anterior aspect of the right knee for eight months Except for some pain there were no other symptoms

CASE 3—Farmer 40 complained of a tumor over the left knee of 14 years duration Examination revealed hydrops of the prepatellar bursa

CASE 4—Farmer 36 had swelling of the right knee for three years An enlarged fluid filled prepatellar bursa was found

(7) J Bone & Joint Surg 36-A 133-139 January 1954

In all four cases the prepatellar bursa was excised and Brucella abortus cultured from tissues taken at operation

The surgical treatment of brucellosis has to do with basic surgical concepts of drainage of infected regions In the authors four cases a fair amount of fibrosis was present in all specimens removed at operation It seems unlikely that any amount of antibiotics would penetrate this protective layer Therefore it appears that medical treatment should be combined with surgical excision of the lesions whenever such excision seems advisable In the present cases in which truly localized lesions were present surgical excision of the lesions was indicated

Antiglobulin Sensitization Test as Applied to Brucella Infection Preliminary Report A A Ferris W J Stevenson and F A Lewis[8] carried out a serologic survey of abattoir workers presumed to be heavily exposed to brucella infection A reported increase in sensitivity of the brucella agglutination test by application of the antiglobulin sensitization technic of Coombs led to its use in this extensive testing to ascertain why the frequency of infection has been lower than would be expected on epidemiologic grounds

Serums were taken from 337 men working in the three main abattoirs of Melbourne The specimens were examined for brucella antibodies by direct agglutination and by the indirect antiglobulin method Serums submitted for Wassermann tests were used as controls

Of the 337 serums of the abattoir workers 10 4% reacted positively to the conventional agglutination test and 47 8% to the antiglobulin test Of the 311 control serums none reacted to the direct agglutination test but 4 5% reacted to the modified Coombs test It was felt that the latter technic is considerably more sensitive than the direct agglutination test for detection of brucella antibody The wide difference between the positive findings in the slaughter house workers who are constantly exposed to brucella infection and the control subjects is strong evidence demonstrating the specificity of the more sensitive technic

[This is a most interesting observation which could have practical value Similar results have been reported from other laboratories in England and in Switzerland I understand that at least one worker in the United States has not been able to get comparable results i e enhancement of sensitivity by means of the Coombs technic.—Ed.]

(8) M J Aust 1a 1 619 621 May 2 1953

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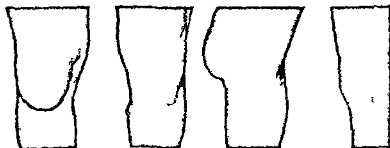


Fig 1—Enla geme t of ght p ep t ll bu sa (Co rte y f Johnso E W Jr and Weed L A J Bo & J t S g 36-A 133 139 Jan ary 1954)

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(7) J Bone & J t S g 36 A 133 139 Janu y 1954

months of negative cultures then there occurred in the 75 children 188 separate clinical cases of shigellosis or an average of 2 5 cases/child/year During the height of the season as many as 25% of the weekly swab cultures were positive for shigella This rate is comparable with that found during clinically defined large scale epidemics of bacillary dysentery in less highly endemic areas

[This is a striking reminder that there are today populations in the world where such sanitary conditions prevail permitting repeated attacks of enteric infection in infants and young children the age group in which shigellosis and salmonellosis are particularly dangerous —Ed]

BACTEROIDES INFECTION

Bacteroides Infections in Obstetrics and Gynecology Bayard Carter Claudius P Jones Robert L Alter Robert N Creadick and Walter L Thomas[1] (Duke Univ) report on 153 patients in whom various species of bacteroides were isolated The bacteroides group is a heterogeneous group of gram negative nonsporulating anaerobic bacilli about which little is known that would allow for practical identification of species The organisms are normal intestinal tract inhabitants of mammals and probably inhabit the upper respiratory and genital tracts

Of the 153 patients 53 were white All had pelvic abscesses at abdominal operations for neoplasms or infections pelvic abscesses drained by colpotomies septicemias pyometra or abscesses from which material could be obtained relatively free from contamination Postpartum or postabortal infections uncomplicated by septicemia or abscess formation were not included as bacteroides is so commonly found in this group

Although the organisms are found on many normal mucous membranes they should not be regarded as harmless as they do cause localized and generalized infections Their significance in anaerobic obstetric and gynecologic infections is not generally appreciated Such infections may complicate malignancies or evolve as pyometra Bartholin abscesses vulvar abscesses septicemia or other types of gynecologic infections

Successful therapy depends on early diagnosis blood

(1) Obst & Gynec 1 491 510 May 1953

SHIGELLOSIS

Incidence of Shigella Organisms in Group of Egyptian Village Children Thomas M Floyd[9] (U S Naval Med Res Unit No 3 Cairo) studied the incidence of shigella organisms by weekly rectal swab cultures in 116 children aged 1 week to 3 years who lived in three villages 30 km north of Cairo The children were of comparable social and economical status Village houses were constructed of mud brick were poorly lighted and ventilated and were usually shared with domestic animals Bathing and washing facilities were inadequate and sewage and garbage disposal facilities were poor Water was obtained from highly polluted canals or from wells often subjected to contamination Cooking facilities were primitive and food was not protected from insects or dust Flies bred in tremendous numbers in human and animal wastes Enteric and diarrheal disease rates were high and between 4 and 6% of the population were enteric carriers About half the subjects had a history of recent diarrhea Owing to deaths changes in residence or non co operation of the mothers the original 116 children was reduced to 75 and these were followed for a year

Positive cultures were obtained from 97 3% of the 75 children Average number from a single child was 3 98 and the highest number 15 Shigella flexneri 2a 3 4a and 5 and S sonnei were the most common types Incidence was low during the winter began to rise during the spring and reached a peak in early summer There was a close correlation between this incidence and the seasonal prevalence of houseflies in Egypt This correlation lends further support to the probability that much of the bacillary dysentery in Egypt is fly borne

Although no correlated clinical observations were made it is possible to estimate the number of cases of bacillary dysentery that occurred in the group If it is assumed that a clinical attack of shigellosis had occurred with each initial isolation of shigella or when a different species or type was isolated no sooner than one month after the previous attack or when the same type or species was recovered after three

(9) Am J T op M d 3 294 302 M ch 1954

nating in renal failure and azotemia served to mask the condition in several of the cases studied

[The author brings out an important clinical point here Particularly likely to be missed are such cases as these occurring in individuals past 45 in whom other diseases of the heart kidneys and lungs are so apt to suggest themselves —Ed.]

Diagnosis and Treatment of Subacute Bacterial Endocarditis Charles K Freidberg[3] (New York City) points out that early diagnosis of subacute bacterial endocarditis is just as urgent as early diagnosis of cancer and offers much more hope of therapeutic success With the increasing use of antibiotics the outlook has improved somewhat but the fatality rate still is between 15 and 25% The importance of early treatment is emphasized by the finding that average recovery rate has been highest among patients receiving adequate therapy early in the disease The rate dropped sharply among those in whom adequate treatment was delayed more than two months

A detailed analysis of fatal cases of subacute bacterial endocarditis indicated that therapeutic failures resulted from errors and especially from delay in diagnosis and that most errors could be avoided by a revision of diagnostic criteria for this disease

Diagnosis can and should be made early i e it should be made on the basis of minimal criteria Painful fingers Osler s nodes and white centered petechiae are included among early symptoms but they often are absent or are overlooked Although the other early symptoms (fever murmur headache malaise pains and anorexia) may be found in almost any infection and in many noninfectious processes they are sufficient to justify the diagnosis of subacute bacterial endocarditis with a high degree of probability Two features unexplained fever for more than a week and an organic cardiac murmur warrant such a diagnosis Most of the common diseases producing fever in a patient with a cardiac murmur subside after 7 10 days or produce evidence of their nature

Some of the commonest erroneous diagnoses responsible for inadequate treatment are grippe or virus infection active rheumatic fever acute lupus erythematosus acute pyelonephritis and cerebral accident Among older patients neoplasm congestive heart failure and cerebral vascular accident may

(3) Am P ct & D g t T eat. 4 444 447 J ly 1953

transfusions good electrolyte balance and adequate drainage In vitro sensitivity studies suggest that aureomycin is more effective than streptomycin penicillin or sulfadiazine Many patients did not respond to any combination of the various agents Thirteen patients died either as a direct result of bacteroides infections or from the adverse effect of the infection on the clinical course of their disease

[Recognition of the importance of this kind of micro-organism is growing steadily Because it is often associated with other bacteria and because laboratory identification of anaerobes is difficult the existence of this type of infection is doubtless often not appreciated The indifferent clinical effect of aureomycin therapy reported by these workers is probably explainable in part by the fact that they were dealing with abscesses where chemotherapeutic agents are always at a disadvantage In other kinds of bacteroides infection aureomycin treatment has usually proved beneficial —Ed]

BACTERIAL ENDOCARDITIS

Difficulties in Diagnosis of Subacute Bacterial Endocarditis Sol Glotzer[2] (Brooklyn) states that there is a relatively large number of cases of subacute bacterial endocarditis in which diagnosis is not made during life or is delayed so long that therapeutic measures are ineffective To learn the reasons for failure of diagnosis he selected records from the autopsy files at Kings County Hospital of eight cases in which a clinical diagnosis had not been made during life The clinical picture permitted classification of cases into three groups cerebral pulmonary and renal

It is felt that severe involvement of a single organ other than the heart or a dramatic symptom complex which focuses attention on such an organ can eclipse the evidences of the underlying heart infection so completely as to make a correct diagnosis not only difficult but impossible In the cases studied subarachnoid hemorrhage meningeal irritation and intracranial lesions masked systemic embolic and cardiac lesions which might otherwise have been detected Pulmonary infection and congestive cardiac failure produced clinical pictures so severe as to occupy the full attention of the observer Involvement of the kidney particularly by diffuse glomerulonephritis in varying degrees is quite common in subacute bacterial endocarditis and the presence of this lesion termi

(2) N w Yo k J M d 53 2796 2800 D 1 1953

early recognition and correct treatment It is in no sense a rare disease being an important cause of death in patients with congenital or rheumatic heart disease In this and the next three articles particular attention should be given to one well established fact nearly all successful results are associated with penicillin therapy singly or in combination with another antibiotic Good results are seldom achieved with the broad spectrum antibiotics Here i a situation in which sensitivity tests may be misleading The chemotherapy must provide bactericidal action not mere bacteriostasis Consequently even though the causative organism may seem more sensitive to another agent in the laboratory test penicillin is generally to be preferred if the organism exhibits any inhibition by penicillin Fortunately there is almost no limit to the dose of that drug —Ed]

Present Day Treatment of Subacute Bacterial Endocarditis is discussed by Chester S Keefer[4] (Boston Univ) The primary insult to the endocardium in all forms of endocarditis is the formation of a thrombus of platelets and fibrin If there are bacteria in the thrombi and they are not killed promptly they grow rapidly and often infect the blood These infected thrombi or vegetations may become massive and may occlude the valvular orifice or there may be rapid destruction of the valve leaflets emboli may be swept into the circulation The course these vegetations take i e along the edge of the valve down into the sinus of Valsalva along the chordea tendinia or along the auricular wall determines the resulting pathologic process and clinical behavior

Vegetations consist of three layers a central necrotic core of relatively acellular fibrillar debris and two layers of bacterial colonies surrounding this central core both layers being covered with a fibrillary material resembling fibrin and platelets It is apparently difficult for leukocytes and anti infective agents to penetrate this barrier When healing of these vegetations occurs it is characterized by calcification organization and valve distortion It is important that the factors promoting healing be better understood Many clinically cured patients who died of other causes have been found at autopsy to have live organisms on the heart valves Cates and Christie report that after death organisms may be cultured from 30% of clinically cured patients There are no absolute methods of determining that healing has taken place other than careful study and follow up of patients

It is important to understand why the organisms in the vegetations can withstand the full impact of chemotherapy

(4) J A M A 15 139 1400 A g 8 1953

be diagnosed without recognition of endocarditis When heart failure has developed in a patient with unexplained fever and a cardiac murmur after onset of the fever a diagnosis of subacute bacterial endocarditis is probable If heart failure precedes the unexplained fever other causes are more likely In adults with rheumatic valvular lesions unexplained fever for more than one week is due to subacute bacterial endocarditis and not to rheumatic fever unless there is frank acute arthritis

Although a variety of other antibiotics is now available penicillin remains the mainstay of treatment Almost all causative nonhemolytic streptococci other than Streptococcus faecalis (enterococcus) are inhibited by less than 0 1 unit/cc medium In practice bacteria of this sensitivity will be eradicated in vivo by daily penicillin doses of 2 000 000 units Although less may be effective in most cases experience indicates that this should be the minimal dose regardless of in vitro sensitivity Proportionately higher doses are required for more resistant nonhemolytic streptococci Endocarditis due to enterococcus is growing in importance as the incidence has increased from about 5 to 20% Here 20 000 000-40 000 000 units of penicillin daily should be given preferably supplemented with 2 Gm benemid® daily given orally in divided doses When combined with 2 Gm daily of streptomycin or dihydrostreptomycin penicillin in lower dosage 6 000 000 10 000 000 units is effective Evidence exists that 10 000 000 units of penicillin with 60 000 units of bacitracin may also be effective in enterococcic endocarditis In selected cases other antibiotics may be the drug of choice

If treatment is started before results of blood cultures are reported or if blood cultures are persistently negative penicillin is given at the rate of 2 400 000 units daily Should the response be unsatisfactory after a few days the dosage is changed to 10 000 000 units of penicillin daily with 2 Gm streptomycin If this is ineffective other antibiotics must be tried

Treatment for four to eight weeks is recommended longer periods are indicated if therapy is delayed

[It may seem to the reader that an inordinately large amount of space is given to the subject of bacterial endocarditis I feel that such coverage is justified because this is a fatal disease if not recognized or not properly treated whereas at least 75% of patients can be cured with

infection rapidly The second patient was treated with chlor amphenicol chlortetracycline and oxytetracycline because the organism Str faecalis was sensitive to these drugs and re sistant to penicillin and streptomycin The infection was not controlled In vitro studies showed that a combination of penicillin and streptomycin was bactericidal while the other antibiotics had bacteriostatic action only Combination of streptomycin and penicillin controlled the infection rapidly

The delay caused by first using bacteriostatic antibiotics was dangerous because major emboli renal failure and irre versible damage to the heart might have occurred

Antibiotic Therapy of Bacterial Endocarditis V Thera peutic Considerations of Erythromycin This drug has been established as a useful antibiotic whose chief value appears to be in the treatment of micrococcic (staphylococcic) infec tions Only a few reports have appeared on its use in bacterial endocarditis and in these results were disappointing Joseph E Geraci and William J Martin[5] describe clinical and labora tory experiences with erythromycin in seven patients with this disease

The authors experience and the observations of others led to the conclusion that erythromycin alone is of little value in the management of bacterial endocarditis and will be of only limited or slight value in treatment when combined with other antibiotics The in vitro studies of Rantz and Randall and of Coleman and associates indicate that erythromycin behaves like the bacteriostatic broad spectrum antibiotics in that it does not often enter into synergistic combination with the bactericidal group of antibiotics In fact antagonism between erythromycin and penicillin has been shown In vitro data at present indicate that erythromycin occasionally behaves syner gistically with streptomycin and bacitracin with regard to certain strains of micrococci and other bacteria the combina tion of erythromycin with one of these antibiotics will be curative occasionally in certain selected ca es of bacterial endocarditis

At present it appears that adequate treatment with the active bactericidal antibiotics penicillin and streptomycin is available for patients who have endocarditis caused by peni cillin sensitive viridans streptococci and by penicillin

(5) P oc Staff M et M y Cl n 29 109 118 F b 24 1954

Weinstein and associates demonstrated that at least two hours is necessary for the concentration of penicillin in the clot to reach that of surrounding tissue fluid Experiments have suggested that penicillin sensitive strains of Streptococcus viridans can survive in fibrin clots after exposure to penicillin concentrations capable of destroying various organisms of the same order of in vitro sensitivity However it is generally agreed that penicillin is the antibiotic of choice for treatment of all sensitive strains of nonhemolytic streptococci and Str viridans and that penicillin and streptomycin should be used in combination for enterococcus endocarditis Occasionally, other combinations of antibiotics are useful in resistant infections

On the basis of study of many patients it has been suggested that the minimal daily dose of penicillin should be at least 2 000 000 units with therapy continued for a minimum of four to six weeks Total duration of therapy is as important as the total daily dose of antibiotics The final decision concerning dosage must rest with the clinical course of the patient Relapses are most common during the first four weeks after treatment is discontinued

Over all results of present treatment can be summed up as follows (1) 60 70% of patients recover from the infection and remain well and asymptomatic for years (2) some die of heart failure uremia or cerebral embolism after recovery from infection (3) about 10 30% die during therapy with signs of active infection heart failure cerebral embolism or hemorrhage and (4) about 2% recover from an initial infection only to have a reinfection later

Bacteriostatic Agents in Treatment of Subacute Bacterial Endocarditis Antibiotics that are purely bacteriostatic have proved disappointing in the treatment of subacute bacterial endocarditis because it is necessary to sterilize the valve lesions For this a bactericidal drug or mixture of drugs is usually required H W Balme and A E Dormer[5] (St Bartholomew s Hosp) report two cases

One patient was treated with oxytetracycline because of severe reactions to penicillin The infection was not controlled although the organism Streptococcus viridans was sensitive Subsequent use of penicillin with antihistamine cleared the

(5) B t M J 1 500 501 F b 27 1954

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serologic reactions the development of miliary calcification and isolation of H capsulatum from the soil at the point source of the epidemic In each of 13 epidemics considered it was possible to find a common place of exposure Never did secondary cases appear in family contacts or associates not exposed to the common source If only the persons intimately associated with the activity at the point source are taken into account the attack rate in each of the epidemics was 90% or higher

Although there was a remarkable similarity in the type of clinical and x ray picture observed in all of the epidemics considerable variation was found in the severity of disease among individual patients Except for generalized histoplasmosis the disease is predominantly a pulmonary infection The nature of the disease and the apparent mode of infection support the theory that the usual mode of infection is by inhalation The recurring story of patients affected was one of exposure to dust created by the agitation of material that had been proved to contain histoplasma spores illness associated with numerous discrete pulmonary infiltrations resulted within one to three weeks of exposure The x ray picture of numerous discrete pulmonary lesions would appear to represent numerous primary lesions caused by the inhalation of a large number of spores with their deposition in many alveoli

[Excellent studies by epidemiologists have established in recent years that numerous outbreaks of pneumonitis previously described by such terms as cave sickness were actually epidemics of histoplasmosis The clinical features mode of infection and distribution of this infection are now fairly well understood —Ed]

Laboratory Infection Caused by Histoplasma Capsulatum

A Nilzen and H Paldrok[7] (Stockholm) describe a bronchopneumonia like picture in seven persons working in a Swedish mycologic research laboratory After the illness each was found to have a positive reaction to histoplasmin

Woman 25 became ill with lassitude chills and muscular pains Temperature of 103 105 F did not abate for six days and she was hospitalized X rays sugg sted bronchopneumonia sparse effu ion in the right pleural cavity and slight enlargement of the right hilar lymph nodes Penicillin was administered for four days but the response was slow One month later some improvement was noted on x ray examination The sedimentation rate remained elevated and the temperature was subfebrile on occasions

(7) A ta d m t 1 33 329 341 1953

resistant streptococci such as enterococci The chief problem in antibiotic treatment of endocarditis is concerned with micrococcic endocarditis as many of the strains of Micro coccus pyogenes in this disease are resistant to penicillin As many as 60 70% of the strains of micrococci recovered from patients who have various infections at present are resistant to penicillin and to a lesser extent to other antibiotics

It was hoped that erythromycin would be as effective in micrococcic endocarditis as it is in micrococcic bacteremia This has proved not to be the case treatment of micrococcic endocarditis with erythromycin results not only in failure but in the fairly rapid emergence of erythromycin resistant organisms

The value of erythromycin in combination with the actively bactericidal antibiotics bacitracin streptomycin or neomycin in treatment of endocarditis caused by penicillin resistant organisms can be determined only by further in vitro testing and by actual treatment of patients Use of eryth romycin in combination with the bacteriostatic broad spectrum antibiotics would not appear justifiable on the basis of avail able evidence except in those rare instances in which in vitro bactericidal tests indicate antibiotic synergism

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HISTOPLASMOSIS

Occurrence of Histoplasmosis in Epidemics Epidemio logic Studies of a group of outbreaks to add to knowledge of the natural reservoir of histoplasma and its transmission to man were reviewed by J Thomas Grayston and Michael L Furcolow[6] (Univ of Kansas) Use of the histoplasmin skin test has disclosed the remarkable geographic distribution of the infection Its wide clinical spectrum from benign to fatal cases has been confirmed by careful clinical and epidemiologic studies A variety of animals infected with Histoplasma cap sulatum have been found and the fungus has been cultured from the soil

Six epidemics reported by others and seven other out breaks found to be of histoplasmosis were studied Diagnosis is based on positive skin reactions to histoplasmin positive

(6) Am J P b H alth 43 665-676 J 1953

again For ultimate evaluation of any method of treatment encouraging initial results are not sufficient

The authors report the successful treatment of seven patients with aureomycin five of whom have been observed for more than two years since completion of therapy No one of the five has shown evidence of recurrence Three with localized cervicofacial actinomycosis were followed for 32 33 and 36 months

In cervicofacial actinomycosis 750 mg aureomycin orally every 6 hours for 10 days and thereafter 500 mg every 6 hours for 18 days are usually effective With bone involvement a greater amount may be required The effectiveness of aureomycin in abdominal actinomycosis has been confirmed In this severe form of the disease prolonged intravenous therapy may be required Supportive therapy in such cases should include maintenance of nutrition as well as fluid and electrolyte balance

An observation period of five years after treatment may be necessary to establish definitely the cure of systemic or visceral actinomycosis Nevertheless on the basis of present studies aureomycin appears to be an effective agent for treatment of the disease

Actinomycotic Pyemia J D Blainey and E O Morris[9] (Birmingham) report a case

Man 50 first noted vague malaise with loss of appetite and weight Seven months later he experienced left sided chest pain followed by fever two weeks later A chest x ray showed some loss of translucency at the left costophrenic angle The fever subsided after a week but he continued to lose weight Six months later he had a further attack of chest pain which improved with penicillin therapy A month later a fluctuant painful swelling appeared in the left arm and was aspirated and several painful whitlows developed Six weeks later a painful swelling appeared in the left calf followed by smaller swellings in the feet and left arm On hospitalization he had a productive cough with abundant purulent sputum Physical examination revealed rales and crepitations over both lung bases The liver and spleen were not palpable A tender fluctuant swelling was present in the left gastrocnemius and a smaller nodule was felt in the muscles of the left forearm There were two flat grayish lesions about 0 2 cm diameter in the skin at the margin of the nail bed on the left hand and larger bluish gray lesions in the skin over the right tibia on the medial surface of the right foot and on the right knee A blood count showed red cell 4 200 000 hemoglobin 88%

(9) Brit M J 2 915 916 Oct 24 1953

Approximately six months later she was rehospitalized Bronchoscopy revealed severe inflammation of the bronchial tree and the mucosa was studded with nodes one of the larger nodes was excised for biopsy This was diagnosed as tuberculosis She had a negative reaction to tuberculin before and after the illness The serum was weakly positive for H capsulatum and results of all other laboratory examinations were normal

Each of the subjects had a positive reaction to histoplasmin 1 100 given intradermally whereas other laboratory workers had negative reactions Retesting of patients at one and three year intervals still yielded positive results Families of the infected persons had negative reactions

The fungus could not be demonstrated in biopsy material or sputum or after other examinations However it is felt that H capsulatum was the causative agent since (1) H capsulatum was the most contagious fungus being handled (2) histoplasmin reactions subsequent to the disease were positive in each affected person but negative in laboratory workers not exposed to the fungus (this is further strengthened by the negative histoplasm reactions in the patient s families and the fact that only 0 6% of eastern Sweden s population is histoplasmin positive) (3) the clinical picture was similar to that in definitely established H capsulatum infections and (4) the coccidioidin reaction was negative in all patients

ACTINOMYCOSIS

Long Term Evaluation of Aureomycin in Treatment of Actinomycosis Because further improvement in the therapy of actinomycosis appeared necessary Leon V McVay Jr and Douglas H Sprunt[8] (Memphis Tenn) in 1949 began a study of the effectiveness of aureomycin in this disease In vitro sensitivity tests on four strains of Actinomyces bovis indicated that this antibiotic had a definite inhibitory effect Initial clinical results were excellent but prolonged observation is necessary for proper evaluation of the treatment Fungous infections are chronic and prone to recur This fact may explain why innumerable agents have been reported as being effective in such disease and then are never heard of

(8) A I t Med 38 955 966 M y 1951

cosis treatment being followed by progressive healing Subsequently various authors described the successful treatment of systemic and cutaneous blastomycosis with stilbamidine and 2 hydroxystilbamidine

Stilbamidine solutions deteriorate rapidly when exposed to light The flasks should therefore be covered with brown or black paper during transport and infusion bottles should be covered during intravenous injections Even a 15 minute exposure to direct sunlight may reduce the therapeutic efficiency of the solution and produce a toxic by product which can cause severe liver and kidney damage Pentamidine propamidine and 2 hydroxystilbamidine do not appear to be affected by ultraviolet light

Patients have received daily intravenous doses of 150-200 mg (2 5 5 mg /kg) stilbamidine in 5% glucose for several weeks without unfavorable reactions The usual maximal daily dose in multiple myeloma and in blastomycosis has been 150 mg The standard dose used in kala azar has been 1 mg /lb or 2 2 mg /kg The total daily dose administered in the author s series varied from 3 5 to 4 6 Gm for adults and was 0 9 Gm for a child aged 4 A continuous course of 30 daily injections (total dose 4 6 Gm) resulted in negative cultures and progressive healing Healing continued slowly but steadily for three months after therapy was discontinued Improvement was much more dramatic in the first and second 30 days after therapy than during therapy Schoenbach has used intermittent therapy (total dose 6 Gm) with good results

Blastomycosis confined to the skin should be treated with vaccines iodides and x rays rather than stilbamidine Patients with disease of the kidneys or liver may show additional damage to these organs after use of the drug This damage may appear three to four months after the last injection Two or more types of liver function tests and renal studies should be performed before treatment is started The only uncontrollable complication of stilbamidine therapy is a peculiar type of neuropathy which usually occurs in the skin area supplied by the sensory portion of the trigeminal nerve In well developed cases there may be paresthesia anesthesia hypalegsia and numbness This complication may appear as early as one month after treatment but usually between the fourth and fifth months It occurs at least in mild

and white cells 7 400 with 89 3% polymorphonuclear leukocytes A chest x ray now revealed diffuse miliary shadowing throughout both lungs The urine was normal Aspiration of the calf abscess produced about 0 5 ml of thick blood stained material containing numerous pus cells and a gram positive filamentous branching organism with many smaller gram negative bacilli

The patient was first treated with streptomycin He remained pyrexial and several new lesions appeared in the extremities After one week 2 000 000 units of penicillin was given daily together with streptomycin The latter was replaced after 14 days with 3 Gm sulphatriad daily in view of isolation of actinomyces israeli from the pus and sputum and the penicillin dose was increased to 4 000 000 units daily Daily injections of 1 000 000 units of penicillin with 2 Gm sulphatriad orally were continued at home for six months The patient has since remained well

Disseminated actinomycosis seems to arise from pulmonary infections since in the more common type of abdominal and cervical lesions localization with extensive fibrosis is the characteristic feature The peripheral lesions in the present case seem to have been confined to muscle subcutaneous tissue and skin for no evidence was found of spread to internal organs This curious localization has been noted in several autopsy reports in the literature

The successful treatment of localized actinomycosis with antibiotics has been widely reported but recovery after pyemic dissemination seems extremely rare

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BLASTOMYCOSIS

Stilbamidine Therapy for Blastomycosis is discussed by David T Smith[1] (Duke Univ) The discovery of the usefulness of stilbamidine propamidine and 2 hydroxystilbamidine in blastomycosis was a by product of a study of the effects of a large series of synthetic aromatic diamidines on trypanosomiasis and leishmaniasis Stilbamidine and propamidine were found to inhibit bacterial growth in much the same manner but less effectively than the sulfonamides In 1945 Elson demonstrated that Sporotrichum schenckii and Blastomyces dermatitidis were inhibited by remarkably low concentrations of propamidine It was not until five years later that the drug (0 1% ointment) was applied locally in cutaneous blastomy

(1) GP 8 69 76 J ly 1953

cosis treatment being followed by progressive healing Subsequently various authors described the successful treatment of systemic and cutaneous blastomycosis with stilbamidine and 2 hydroxystilbamidine

Stilbamidine solutions deteriorate rapidly when exposed to light The flasks should therefore be covered with brown or black paper during transport and infusion bottles should be covered during intravenous injections Even a 15 minute exposure to direct sunlight may reduce the therapeutic efficiency of the solution and produce a toxic by product which can cause severe liver and kidney damage Pentamidine propamidine and 2 hydroxystilbamidine do not appear to be affected by ultraviolet light

Patients have received daily intravenous doses of 150 200 mg (2 5 mg /kg) stilbamidine in 5% glucose for several weeks without unfavorable reactions The usual maximal daily dose in multiple myeloma and in blastomycosis has been 150 m The standard dose used in kala azar has been 1 mg /lb or 2 2 mg /kg The total daily do e administered in the author s series varied from 3 5 to 4 6 Gm for adults and was 0 9 Gm for a child aged 4 A continuous course of 30 daily injections (total dose 4 6 Gm) resulted in negative cultures and progressive healing Healing continued slowly but steadily for three months after therapy was discontinued Improvement was much more dramatic in the first and second 30 days after therapy than during therapy Schoenbach has used intermittent therapy (total dose 6 Gm) with good results

Blastomycosis confined to the skin should be treated with vaccines iodides and x rays rather than stilbamidine Patients with disease of the kidneys or liver may show additional damage to these organs after use of the drug This damage may appear three to four months after the last injection Two or more types of liver function tests and renal studies should be performed before treatment i started The only uncontrollable complication of stilbamidine therapy is a peculiar type of neuropathy which usually occurs in the skin area supplied by the sensory portion of the trigeminal nerve In well developed cases there may be paresthesia anesthesia hypalgesia and numbness This complication may appear as early as one month after treatment but usually between the fourth and fifth months It occurs at least in mild

form in a large percentage of cases Two patients with blastomycosis have been treated successfully with 2 hydroxystilbamidine without development of peripheral neuropathy

Acute Blastomycotic Pneumonia Report of Fatal Case of Short Duration Diagnosed by Needle Biopsy of Lung is presented by Lowell H Steen Donald T Foxworthy and Lyle A Baker (V A Hosp Hines Ill)

In man 36 after two months of chills fever cough and weakness the fever abated with penicillin therapy but sputum ejection

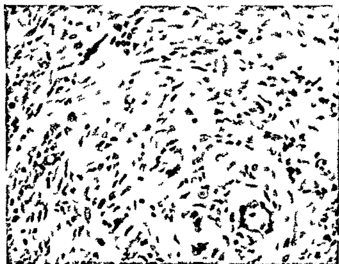


Fig 2—Bl t my o s of l ng (p t n b op v sp m n) (Court sy of St n L H *et al* A M A A h I t M d 93 464 472 M h 1954)

and dyspnea continued Due to acute illness he was hospitalized with fever of 101 8 F pulse rate 116 and respiratory rate 28 Signs of pneumonia were noted in the left side of the chest White blood cell count was 30 000 and hemoglobin content 7 5 Gm Chest x ray disclosed patchy infiltration and suggestive nodular densities in the right lung and homogeneous infiltration obscured the lower half of the left Later posteroanterior and left lateral Bucky x rays disclosed consolidation of the lower lobe of the left lung Subsequent examinations indicated rapid progression of lesions X rays taken 29 days after hospitalization disclosed extensive nodular infiltration and severe progression of the patchy infiltration in the right lung

Penicillin and chlortetracycline therapy produced no response

(2) A M A A ch I t M d 93 464 472 M h 1954

Thoracentesis was unsuccessful Cell blocks obtained on bronchoscopy contained no tumor cells Fever continued his status became critical and severe dyspnea required oxygen therapy Whether the downhill course was due to secondarily infected malignant tissue or to primary bacterial or fungous infection that might be amenable to therapy could not be established Aspiration biopsy of the lower lobe of the left lung on the 23d hospital day disclosed blastomycosis (Fig 2) He died six days later Autopsy confirmed bilateral fulminant pulmonary blastomycosis

Aspiration biopsy may be applicable to any pulmonary disease of undetermined origin

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SYPHILIS

Clinical Value of the Treponema Immobilization Test in Diagnosis and Control of Syphilis is discussed by C W Chacko[3] (St Mary s Hosp London) False positive reactions given sometimes by both complement fixation and flocculation tests have not been completely eliminated by improvements in the methods and materials Attempts to grow virulent Treponema pallidum in artificial culture medium and thereby provide sufficient specific antigen for serologic tests have hitherto failed However a new approach to the problem was made when Nelson and Mayer (1949) devised the pallidum immobilization (TPI) test for syphilis Virulent T pallida were extracted from rabbit testes into a special anaerobic medium in which they were kept alive and virulent for several days This relatively tissue free suspension of mobile T pallida was immobilized when mixed with syphilitic serum in vitro in the presence of active complement No such immobilizing effect was obtained with normal or serologically false positive serums or in the absence of fresh complement Since a virulent strain of T pallidum was used the TPI test was considered a specific test for syphilis involving a specific antitreponemal antibody This antibody was demonstrated to be distinct from the Wassermann antibody which could be absorbed from the syphilitic serum with lipoidal tissue extract antigen leaving the immobilizing antitreponemal antibody intact

In the present study 532 specimens of blood serum and 56

(3) J Cl P th 6 2 7 31 A g t 1953

of cerebrospinal fluid from syphilitic and nonsyphilitic persons have been examined with four tests in parallel namely the TPI test the Wassermann test the Kahn test and the Venereal Diseases Reference Laboratory U S P H S (VDRL) slide flocculation test

It has been found that the TPI test is sensitive enough to detect syphilis in all stages beyond its early primary stage Results of the TPI test remain positive indefinitely in syphilis after adequate treatment unless treatment is started very early whereas results of standard tests usually yield to treatment A positive TPI test at its present stage of development would mean that the patient has or has had syphilis and the findings with this test may not be used as a criterion for cure or in the control of treatment

The TPI test has been rarely positive in normal persons or in diseases other than syphilis except those due to treponemas Thus unlike the standard tests in current use it appears highly specific Its greatest value at present would be as a verification test for the biologic false positive reactions obtained with standard tests The TPI test is also sensitive and specific in the examination of cerebrospinal fluid in syphilitic cases as well as in manifestations characteristic of late syphilis e g aortitis where the results of standard tests are negative

[Experience with this technically difficult test has varied and there is some disagreement about its practical value The weight of opinion seems to swing in favor of its specificity and reliability Its greatest practical value would seem to be in the revelation of false positive results of tests for syphilis by other technics Unfortunately this test is not yet generally available to American physicians —Ed]

Venereal Diseases—Present and Future According to Nicholas J Fiumara[4] (Massachusetts Dept of Pub Health) there has been a steady decline in the United States beginning with 1948 in the reported cases of gonorrhea and syphilis among the civilian population The sharpest drop a rate decline of 85 9% occurred in the reported cases of lesion syphilis the primary and secondary stages of the disease Although these are the reported cases and rates for gonorrhea and syphilis they do not actually represent the true incidence of the diseases because in many instances syphilis is not found until it has progressed to one of the late stages thus repre

(4 Am J P b H lth 43 1443 1451 N mbe 1953

senting a missed early case Often enough the disease may escape detection completely Gonorrhea in the female is frequently more difficult to detect both by patient and physician For both gonorrhea and syphilis there is the increasing problem of incomplete reporting The best estimate of the incidence of syphilis indicates that for 1952 there were 110 000 new cases The incidence of gonorrhea is felt to be at least five times that of syphilis This estimate may have to be revised upward

The basic causes in reduction of both gonorrhea and infectious syphilis include first the organization and efficient functioning of venereal disease control activities throughout the United States Second the effect of penicillin is rapidly reducing the infectiousness of both diseases Unfortunately modern diagnostic methods have not kept pace with but have actually lagged behind the speed of therapeusis It frequently takes a longer time to diagnose than to cure

Present day clinical management has caused a shift back to ambulatory treatment The ease of clinical management and relatively low cost of treatment has brought patients more and more to private medical care However the problem of nonreporting on the part of private physicians has been greatly accentuated Doctors do not have the time to interview patients for contacts therefore health departments should offer the services of trained interviewers to private physicians

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LEPTOSPIROSIS

Acute Leptospira Pomona Arthritis and Myocarditis A case of acute arthritis and myocarditis associated with specific serologic reactions of leptospirosis due to Lept pomona is reported by W D Sutliff Roberta Shepard and Wolcott B Dunham[5] (Memphis Tenn) Resemblance to rheumatic fever was sufficiently close to require specific differential methods and the clinical picture was one not described before in leptospirosis Both joint pains and myocardial damage have been described as minor features of leptospirosis and pains in the muscles particularly of the lower extremities appear to be common

(5) A n I M d 39 134 140 J ly 1953

Man 37 was hospitalized after an illness of one week that started as nonproductive paroxysmal coughing not related to exertion one day later, while playing baseball his left ankle became painful and swollen During the day fever and malaise developed and during the succeeding week he had a migratory type of joint pain involving the knees ankles wrists and shoulders Swelling of the left ankle persisted until hospitalization

He had a flushed face mild conjunctival injection swelling of the eyelids and generalized patchy erythema of the upper trunk Respirations were rapid labored and shallow Temperature was 102 F pulse 120 Fine inspiratory rales were present at the lung bases Positive results of agglutination tests with Lept pomona were given by serums obtained on the 14th and 21st days of illness when diluted 1 4 096 The titers of subsequent serums declined being 1 024 on the 35th day 256 on the 43d and 49th days and negative on the 99th day after onset Weak cross agglutinations were obtained with Lept canicola during the height of the infection

The ECG on admission was normal but changes indicating pericarditis or myocarditis appeared and then returned to normal at the time of discharge The erythrocyte sedimentation rate remained elevated until the 26th day of illness when it decreased to normal at discharge 51 days after the onset of his illness

The symptomatology was unusual when compared with typical leptospirosis in that joint pains with obvious swelling and redness of one joint precordial distress enlargement of the cardiac shadow ECG changes of myocarditis and pulmonary congestion and respiratory distress dominated the picture The patient's story of migratory joint pains led to a diagnosis of rheumatic fever However because of the clinical impression based on conjunctivitis and swelling of the eyelids the bandlike headache and vomiting the possibility of leptospirosis was considered Serologic agglutination tests were pathognomonic of Lept pomona infection Exposure to pigs carried in a closed automobile driven by the patient is suspected as the source of infection

[Relatively few cases of infection by Lept pomona have been recognized in America but doubtless many have been missed Most of the others have taken the form of grippelike illness with or without signs of meningeal irritation This one is of interest because it simulated acute rheumatic fever —Ed]

Pulmonary Manifestations of Leptospirosis. During the past decade leptospiral infections have received much attention due to their prevalence protean manifestations and importance as a public health problem The pulmonary changes in leptospirosis are usually only incidental findings representing part of the widespread involvement by this disease Occa

sionally however hemorrhagic pneumonitis may be an early or predominant clinical manifestation presenting a bizarre diagnostic problem Charles M Silverstein[6] (Atlanta Ga) reports two typical cases

CASE 1—Youth 20 was bitten by a rat two weeks before hospitalization He complained of chest pain cough and sore neck He did not appear ill Physical examination showed slight conjunctivitis

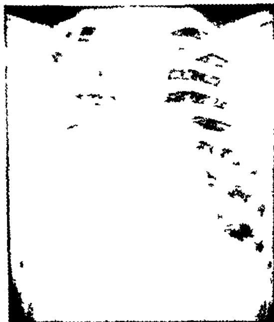


Fig 3—Roentgenogram how g filt t o s becom g flu t in r ght l wer che t (Co rt sy of S l t n (M Rad logy 6 32 334 S pt mber 1953)

questionable stiffness of the neck but no icterus Breath sounds were diminished and scattered crackling rales were heard The sputum was grossly bloody The temperature was 101 F A chest roentgenogram revealed numerous small pulmonary infiltrations 3 or 4 mm in diameter which were uniformly disseminated with no tendency to confluence Urines were repeatedly normal The red blood cell count was 3 600 000 with 12 4 Gm hemoglobin The white cell count was 8 850 with 73% segmented forms The icterus index was 12 units Multiple sputum and blood cultures were negative On the second hospital day he appeared extremely ill Whereas the

(6) Radiology 61 3 2 334 September 1953

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icteric skin stiff neck and rales over both lung fields posteriorly together with costovertebral tenderness The urine showed albumin and granular casts The initial white blood cell count was 6 500 rising three days later to 12 000 with 90% neutrophils The cerebro spinal fluid four days after admission was xanthochromic with 180 white blood cells 89% being lymphocytes A chest roentgeno gram (Fig 4) showed small miliary patchy infiltrations throughout the lower three quarters of both lung fields After three days of penicillin treatment the temperature became normal (from 103 105 F) and he made an uneventful recovery

The pulmonary changes in leptospirosis consist chiefly of hemorrhagic pneumonitis Microscopic examination reveals no evidence of a primarily inflammatory process although there may be areas of leukocytic infiltration and active phago cytosis Spirochetes have not been recovered from the lungs

The roentgen manifestations may consist of (a) small patchy localized infiltrations which have the appearance usually ascribed to bronchopneumonia or more linear or segmental infiltrations such as are seen in atypical pneumo nia (b) confluent larger areas of consolidation which have the appearance of pneumonia pulmonary edema or paren chymal hemorrhage or (c) widely disseminated small infiltra tions Postmortem examination in two cases demonstrated that the radiographic findings which were interpreted as pneumonia were due to pulmonary hemorrhage and edema

Benign Aseptic Meningitis Due to Leptospira Grippoty phosa In November 1952 Spain and Howard reported the first case of leptospirosis due to Lept grippotyphosa (mud fever) in the United States Roy S Bigham Jr [7] (U S Air Force) reports another the clinical course of which is per haps more typical of the infection as described elsewhere than that in the case reported by Spain and Howard

Man 25 began to have intermittent left flank pains on July 6 1952 One week later the pain became steady and severe Chills fever generalized aching and frequent urination developed and he was hospitalized for observation The leukocyte count was 16 000 with 93% neutrophils and 7% lymphocytes Results of physical ex amination were normal except for tenderness over the left renal area and temperature of 103 6 F Penicillin and aureomycin were admin istered and the patient became afebrile and asymptomatic on the second hospital day He was discharged on the fourth day with a diagnosis of acute left pyelonephritis

The day after discharge 12 days after onset of initial symptoms

(7) A M A Arch Int Med 92 587 590 Oct 1953

physical findings suggested consolidation in the right middle and lower lobes the chest roentgenogram (Fig 3) showed considerable increase in the small disseminated infiltrations which became somewhat confluent in the right lower chest Chlortetracycline was added to the initial penicillin treatment On the third day signs of meningeal irritation and stupor developed The cerebrospinal fluid had a ground glass appearance with 880 white blood cell 92% polymorphonuclear leukocytes and 127 mg % protein Streptomycin wa added to the medication penicillin being discontinued The fol



F g 4 —Cl w f th m l y le s (ght l we l ng) (Cou t y f Sil te n C M Rad l gy 61 3 7 334 S p mb 1953)

lowing day he looked and felt well the hemoptysis had ceased and the neck was only slightly stiff The temperature became normal and an uneventful recovery set in Two days after the fastigium the chest roentgenogram revealed clear lung fields On the same day the agglutination titer for Leptospira icterohaemorrhagiae was 1 800 and for L canicola 1 1 600 a week later the titers rose to 1 1 600 and 1 3,200 respectively

CASE 2 —Man 31 had experienced back pain three weeks before hospitalization then fever 10 days later followed in a few days by nausea vomiting epistaxis and hemoptysis Finally jaundice developed and he became drowsy Physical examination revealed

rounded somewhat contracted form Maximal immobilizing effect was observed after 20 30 minutes the amebas gradually regaining their activity thereafter

Immobilization of E histolytica by rabbit antiserum differs in certain essential characteristics from the corresponding reaction between T pallidum and its antibody In the case of the treponeme loss of motility appears to be irreversible In the studies with amebas there was early recovery of immobilized trophozoites It appears that complement which is important in the treponeme reaction may not be essential in immobilization of amebas

Serious consideration should be given to practical applications of the reaction as a diagnostic aid Any method which can demonstrate a serologic response to E histolytica may assist in establishing the etiologic agent in obscure clinical illness The simplicity and reproducibility of the present technic suggest its early evaluation

[If this test turns out to be specific it will have practical value since the complement fixation technic for amebiasis has not proved reliable being subject to both false positive and false negative results —Ed]

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4 TOXOPLASMOSIS

Benign Acquired Toxoplasmosis with Subsequent Pregnancy The first reported cases of toxoplasmosis were of fatal disseminated disease in newborn infants and adults It soon became evident that fatal toxoplasmosis in the newborn was not uncommon but mothers of these infants showed no clinical evidence of infection This led to the belief that the disease must occur in a mild or asymptomatic form Only recently evidence for such a benign infection has been reported The development of a satisfactory test for toxoplasma antibodies and its systematic use in certain areas have indicated that benign toxoplasmosis may occur rather frequently without systemic manifestations

Mearl F Stanton and Henry Pinkerton[9] (St Louis Univ) describe a case of benign toxoplasmosis in which positive serologic findings were supplemented by visualization of organisms in an excised lymph node It is of special interest since it occurred in a woman who gave birth to an apparently

(9) Am J Cl P th 23 1199 1 07 D mb 1953

he noted a mild bilateral frontal headache This became worse and three days later he was rehospitalized Temperature was 100 F and he had a moderately stiff neck with pain in the neck and back when anteflexion of the head was attempted No other abnormal physical findings were present and a diagnosis of poliomyelitis was made.

The patient had never been out of the United States and had no previous illness There was no specific history regarding animal or contaminated water contacts

The cerebrospinal fluid was examined on admission and at the end of the first and second weeks All pressures were less than 16 cm water and the dynamics were normal The initial cell count was 280 the second 98 and the last 21 cu mm Lymphocytes only were present on all counts The initial cerebrospinal fluid protein was 101 75 mg and the final determination 64 8 mg /100 cc

Serologic studies established the disease process as leptospirosis due to Lept grippotyphosa six weeks after the patient was dis charged with a diagnosis of nonparalytic poliomyelitis Complement fixing antibodies for lymphocytic choriomeningitis and mumps were absent A serum specimen on July 31 showed an agglutination titer for leptospirosis of 1 6 400 and a specimen on August 30 a titer of 1 1 600 Absorption of the serum with Lept grippotyphosa indicated this to be a specific reaction

Leptospiral infection in the United States has probably been obscured by the dominant interest in Weil s disease and by a dearth of diagnostic facilities However the index of suspicion for leptospiral infections is high among epidemiolo gists and more reports will appear as clinicians become more aware of the diseases

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AMEBIASIS

Immobilization of Endameba Histolytica in Vitro by Anti serum Produced in the Rabbit. The demonstration that syphi litic infection produces antibody which immobilizes Trepo nema pallidum suggested to Berwin A Cole John F Kent and Victor A Lopez[8] (Walter Reed Army Med Center) the possi bility that ameba immobilizing antibody might appear after infection with E histolytica

Experiments showed that serums from rabbits inoculated with E histolytica plus Trypanosoma cruzi regularly immo bilized amebas of the same strain cultured with mixed bac teria as commensals When mixed with antiserum motile trophozoites ceased formation of pseudopodia and assumed a

(8) Proc Soc. Expe B i & Med 83 811 814 A g Sept. 1953

bodies indicate its prevalence in many species of animal and man By adult life probably between one fourth and one half the population is infected Women who bear toxoplasmic infants have the disease in latent form usually with a high titer of antibodies but rarely have clinical manifestation the disease There are two main types of active toxoplasmosis In the first the course is benign lymphadenitis is the most prominent feature and glandular fever may be closely simulated In the second the disease is severe and often fatal and resembles a typhus like illness with high fever and a diffuse maculopapular rash

CASE 1—Man 21 complained of severe headache general malaise and limb pains Temperature was 103 F and glands in the posterior triangle of the neck and in the axillae were enlarged and tender White blood cell count was 9 800 10% of the monocytes were abnormal suggesting glandular fever but results of the Paul Bunnell test were negative One year later he had enlarged lymph glands in the neck and axillae The cytoplasm modifying (dye) test for toxoplasmosis was 1 9 000 the complement fixation test was 1 32 1 64 ± and the toxoplasmin skin test gave strongly positive results

CASE 2—Boy 15 had enlarged painless lymph glands in the occipital and posterior sternocleidomastoid areas of the neck and in the left axilla White blood cell count was 9 000 with 55% lymphocytes many of which were abnormal resembling Downey cells types I and II Paul Bunnell results were negative He was afebrile and the enlarged glands rapidly diminished and disappeared after a year During observation over several months the cytoplasm modifying toxoplasmosis test was first 1 12 800 then 1 6 400 then 1 8 000 and finally 1 1 020 The complement fixation test changed from 1 80 1 60 ± to 1 16 1 32 ± The skin test gave strongly positive results It was not possible to infect mice with toxoplasmosis by using the patient s blood

CASE 3—Woman 48 had headache generalized muscular pains intermittent pain in the right side of the chest sore throat and fever for one week and epigastric pain for two days She was delirious temperature was 102 F pulse rate 140 respiratory rate 28 and the entire body except for the face was covered with a maculopapular rash. The Paul Bunnell test and agglutination tests for typhoid paratyphoid nonspecific salmonella and Brucella abortus gave negative results Although the pyrexia diminished with penicillin therapy low grade fever back and leg pains and rash continued for several months She improved slowly and was clinically well after six month She had low titer antibodies in the Weil Felix reaction which did not rise during a four month period of observation indicating that she probably did not have Brill s disease At the beginning of her illness the cytoplasm modifying test for toxoplasmosis was 1 64 and during a four week period it was 1 294

normal child 36 weeks later Presumably it is this benign acquired form of toxoplasmosis that occurs in women who give birth to infected infants

Woman 26 was hospitalized for diagnostic excision of an en larged cervical lymph node which had appeared seven weeks pre viously The enlargement had appeared rapidly following what was described by the patient as an attack of sinusitis Several cervical nodes could be palpated at the onset of symptoms however only one enlarged node persisted

Examination revealed an apparently healthy patient The mass measured $3 \times 2 \times 1$ cm and was not firmly attached to surrounding tissues It was excised and proved to be an enlarged lymph node She was asymptomatic during her short stay in the hospital After *leaving the hospital she had monthly physical examinations and* serologic tests She remained free from symptoms and delivered a normal full term male infant 36 weeks after the node was excised The child showed normal development and good health when seen at 10 months

The excised lymph node showed florid granulomatous reticulosis throughout with little regard for lymphoid architecture Histologic study revealed a toxoplasma pseudocyst or terminal colony in the peripheral sinus of the node Only one other definite aggregate of organisms was found in the entire lymph node

The Sabin Feldman serum dye test was used to study the ero logic reactions to the toxoplasma organism throughout the preg nancy The first serum drawn approximately 14 weeks after onset of cervical lymphadenopathy showed a titer of 1 1 024 for toxoplasma antibodies Subsequent dye tests done at 18 29 and 36 weeks re vealed respective titers of 1 1 024 1 1 024 and 1 1,256 By the time of delivery the titer in the serum dye test had fallen to low values

A high stationary titer may indicate only that an indi vidual was at one time stimulated to produce antibodies but a decline *in titer over a period of nine months seems to indi* cate recovery from a recent mild infection

[A well studied and convincing case Very probably some of the puzzling pictures of indolent cervical adenitis that we see in young adults are examples of this benign form of toxoplasmosis Danish and British workers have reported cases in which the clinical picture simulated in fectio s mononucleosis (See next article)—Ed]

Acquired Toxoplasmosis *With Report of Two Cases* Simulating Glandular Fever and One Possible Case Resem bling Typhus Eric Skipper J K A Beverley and C P Beattie[1] (Univ of Sheffield) state that acquired toxoplasmosis occurs in both latent and active forms The latent form is *more* common and erologic surveys for toxoplasma anti

(1) La t 1 287 290 Feb 6 1954

bats is deranged behavior during which time they may bite other animals

The paralytic form of rabies is usually seen in cattle in fected by bats It is characterized by an initial period of rest lessness and excitement followed soon by paralysis of the rear quarters

Symptoms in human beings appear suddenly usually three to four weeks after the bite of an infected bat The first complaint i usually a burning or tingling sensation in the bitten limb and there may be paresis in the limb at onset of the disease The patient is febrile and often has a headache Following these prodromal symptoms which may last one to four days muscular weakness progresses to complete paralysis of the limb The trunk muscles and arms are soon involved terminating in a fatal paralysis usually about the seventh day after onset of symptoms

Control activities should be directed toward destruction of vampire bats or any other bat known to harbor and transmit rabies virus Bat populations near villages or thickly popu lated areas can be successfully limited by destruction of the colonies Limiting the bat populations in sparsely settled re gions where livestock range over large areas is more difficult and sometimes almost impossible

The circumstantial evidence of bat rabies in southern California the spread of derriengue in Mexico and the recent recognition of rabies infection among insectivorous bats in Florida and Pennsylvania may lead to a change in the con cept of a bat rabies problem in the United States Because the habitat of the vampire bat is limited by temperature require ments to a warm climate it is not likely that this bat will present a problem in the United States except perhaps in the southern fringe of the country

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VIRAL MENINGITIS

Problem of Aseptic Meningitis According to Ivan L Ben nett Jr [3] (Yale Univ) the syndrome of aseptic meningitis is characterized by fever stiff neck pleocytosis negative rou

(3) GP 8 45 50 O t be 1953

1 300 and 1 260 three months later it was 1 53 On the same dates the complement fixation test titers were anticomplementary—1 2 1 4± 1 8 1 16± 1 18 1 16± and 1 10 The toxoplasma parasite could not be isolated in mice

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RABIES

Bat Rabies The recognition of rabies infection in insectivorous bats is an interesting and significant discovery which according to Robert D Courter (Atlanta Ga) may have far reaching implications as a new public health problem in the United States

The existence of rabies infection in bats of the United States was unknown until June 1953 when it was discovered by the Tampa regional laboratory of the Florida State Board of Health The first bat found to be infected was a Florida yellow bat (Dasypterus floridanus) which had been killed while attacking a boy Later the rabies virus was found in the brains of five more yellow bats and one Seminole bat (Lasiurus seminola) which had been killed in flight while feeding In September 1953 Dr Ernest Witte Pennsylvania State Department of Health reported rabies infection in a bat which made an unprovoked attack on a woman

The existence of rabies among bats was first recognized in Brazil in 1908 Pawan cited Carini s discovery in 1911 of Negri bodies in the brains of cattle dying of a paralytic disease which was epizootic in the state of Santa Catarina The disease spread to Trinidad in 1925 Four years later in Siparia in southern Trinidad there was an epidemic of ascending paralytic myelitis in human beings which Hurst and Pawan found to be caused by the rabies virus The same disease continued to spread to Mexico Honduras and Venezuela

The rabies virus isolated from bats has been shown by pathologic study animal inoculation and complement fixation cross neutralization and protection tests to be closely related to classic strains of rabies virus

Bat rabies occurs in nature in human beings herbivorous animals and hemophagous and frugivorous bats Rabid dogs have been seen frequently in areas where bat rabies was epizootic The predominant symptom observed in frugivorous

(2) P b H lth Rep 69 9 16 J y 1954

early in aseptic meningitis effectively rules out mumps a negative skin test indicates susceptibility but is not diagnostic

Serum collected during the acute illness should be saved in every case of aseptic meningitis so that it can be tested at the same time convalescent serum is examined and the presence of a rising titer determined Heterophil antibodies establish the diagnosis of infectious mononucleosis and a rise in serum agglutinins is demonstrable in leptospiral infections Mumps lymphocytic choriomeningitis and the various encephalitides (except encephalitis lethargica) can be diagnosed by complement fixation tests Recently two promising technics a complement fixation test and isolation of the virus through the use of tissue cultures have made diagnosis of poliomyelitis possible

Aseptic Meningitis a Disease of Diverse Etiology Clinical and Etiologic Studies on 854 Cases Sporadic cases of infection of the central nervous system presumably of virus origin contribute much of the material received by a virus diagnostic laboratory Charles V Adair Ross L Gauld and Joseph E Smadel[4] analyzed material of this type submitted to the department of virus and rickettsial diseases of the Army Medical Service Graduate School over 11 years from military personnel veterans and their dependents in the United States Almost all of the patients presented clinical findings resembling the syndrome designated by Wallgren as acute aseptic meningitis

Approximately 9% of the cases were caused by infection with *lymphocytic choriomeningitis virus* and 12% with mumps virus Recent studies on some of the cases indicate that the herpes simplex virus was responsible for about 5% and leptospires for about 7% However no specific etiologic agent was incriminated in approximately three fourths of the cases The application of newly developed diagnostic procedures and the more extensive use of available diagnostic technics may be expected to reduce the size of this undiagnosed group

[It is a little discouraging to realize that we can determine the etiology in only a quarter of these cases at present —Ed]

Port Augusta Meningitis Observations in an epidemic of aseptic meningitis in Port Augusta in South Australia are dis

(4) A I t M d 39 675 704 O t b 1953

tine culture no neurologic signs and normal cerebrospinal fluid glucose

The manifestations of diseases which must be considered in differential diagnosis are so similar that distinction be tween them clinically is ordinarily almost impossible Even with the best of special laboratory aids including virus isola tion technics and serologic testing of convalescent serum *many cases remain undiagnosed History of the season of the* year during which illness occurs may be helpful

A careful description of symptomatology preceding onset of meningeal signs may be of value Poliomyelitis and lympho cytic choriomeningitis are biphasic illnesses The biphasic character of the latter disease may not be appreciated unless it is realized that the first phase of the disease (consisting pre dominantly grip like upper respiratory symptoms) is pro longed A history of exposure to various animals may give some hint Mice are the reservoir of lymphocytic choriomenin gitis Dogs rats and swine are carriers of leptospirae Aseptic meningitis in a pregnant woman is likely to be poliomyelitis

Careful search for a rash is important infectious mono nucleosis and leptospirosis are most likely to produce skin eruptions Lymphadenopathy or pharyngitis is suggestive of infectious mononucleosis Tenderness and enlargement of the submaxillary salivary glands or testes point to mumps in pa tients with aseptic meningitis Conjunctival suffusion is com mon in leptospirosis whereas hepatomegaly and splenomegaly suggests virus hepatitis or infectious mononucleosis Close attention to reflexes muscle strength and the presence of muscle spasm is necessary for early recognition of acute poliomyelitis

The presence of atypical cells in the blood may be helpful in making a diagnosis of infectious mononucleosis Early cere brospinal fluid examination reveals a considerable number of polymorphonuclears but mononuclear cells soon predominate It is unusual to find more than 300 cells in leptospiral menin gitis a cell count of over 500 virtually rules out poliomyelitis and a count of 2 000 3 000 with 98 100% mononuclear cells is diagnostic of lymphocytic choriomeningitis The cerebro spinal fluid glucose is normal There is now available a skin test antigen for mumps which produces a delayed tuberculin like reaction in patients with the disease A positive skin test

Varicella Encephalitis Emanuel Appelbaum Morton H Rachelson and Vera B Dolgopol[6] (New York City) summarized experience with 59 cases of varicella encephalitis seen over 20 years Reliable statistical information about the incidence of varicella encephalitis is not available The recorded incidence of 0 26% of 6 774 varicella cases at Willard Parker Hospital is probably too high because patients are usually admitted to this contagious disease hospital for severe disease The true incidence of varicella encephalitis is probably less than that of measles encephalitis which has an incidence of less than one case per thousand

Sixty five per cent of the cases occurred between the third and eighth posteruptive days In half the cases onset was acute with headache vomiting fever changes in sensorium convulsions and paralysis The clinical picture represented acute meningoencephalitic involvement The clinical course was variable and almost every symptom or sign indicative of central nervous system involvement was encountered Frequent changes in sensorium occurred early in the disease Cerebrospinal fluid examinations generally showed clear fluid under moderately increased pressure A moderate numerical increase in white cells was the most common abnormal finding and in only 10 instances was the pleocytosis more than 100 cells/cc lymphocytes usually predominated

Three of the 59 patients died a mortality rate of 5% each death occurred within the first week of illness When discharged from the hospital 47 patients (80%) had no neurologic or other detectable abnormalities Nine had such residua as paralysis ataxia blindness mental retardation disturbance of speech and personality changes Follow up observations reveal that although in most instances the neurologic pattern is well defined at the time of discharge significant changes in the patient s status may occur with the passage of time

No specific therapy was used but it was suggested that in the early phase of encephalitis the use of corticotropin or cortisone would seem worth while since these drugs have been shown to suppress experimental demyelinating encephalomyelitis No significant prognostic factors were noted Though a favorable outcome may be anticipated in the vast majority

(6) Am. J M Sc 15 225 230 Aug 1953

cussed by J A R Miles and D M Surrey Dane[5] (Adelaide) Except for one fatal case the disease was mild and of short duration The fatality occurred in a mongol aged 13 months from whose brain a virus was isolated which was probably responsible for the epidemic

Because of a report that hamsters pretreated with corti sone show a greatly increased susceptibility to infection with type 2 poliomyelitis virus six 3 week old cortisone treated mice were inoculated intracerebrally and intraperitoneally with prepared brain suspension The material was passed as a 20% suspension to further cortisone pretreated mice for four passages and the fifth passage was found to kill normal mice in approximately the same time that it killed the cortisone treated animals

The virus is large It passed through membranes with an average pore diameter of 750 or 600 mμ but not through a membrane with an average pore diameter of 390 mμ Smear of yolk sac heavily infected with virus when stained by Giemsa or Machiavello s stain showed numerous round bodies of the order of size expected They looked not unlike the elementary bodies of the psittacosis group viruses However the virus is not serologically related to psittacosis It was resistant to penicillin and streptomycin and failed to grow on a variety of bacteriologic mediums under several different conditions

The pathogenicity pattern of the virus is peculiar in that it causes meningitis and myositis in mice but more readily in weaned than in suckling animals It also causes myositis in guinea pigs In man the virus may apparently cause menin gitis and at least in the laboratory inapparent infection with development of complement fixing antibodies It is unrelated serologically to mumps and lymphocytic choriomeningitis and at present cannot be placed in any of the recognized groups

High titers were not found in any serums but in three of six cases occurring at the same time as the fatal one and thought to be from the same epidemic a rising titer was found In two others antibody was present in both early and late serums Results of complement fixation tests on serums of patients affected in the same outbreak as the patient who died suggest that this virus caused the epidemic

(5) M J A t al 1 884 886 J 20 1953

130 volunteers Parallel cultures not inoculated with infective material did not give rise to colds in 61 volunteers However the incidence of colds produced by D C culture materials (10%) was lower than that following administration of nasal washings from subjects with colds (29%) The proportion of colds produced by infected nasal washings has varied from year to year but no explanation for this has been found Furthermore it was not possible to differentiate clinically between colds produced by culture materials and those produced by nasal washings

Colds were induced by cultures up to and including the 10th serial culture At each passage a 3 fold serial dilution occurred and by the 10th serial culture the original virus had survived 35 days at 37 C and had undergone a 10^5 fold dilution Culture materials were further diluted 1 5 before testing No colds have been produced with an infected nasal washing diluted more than 1 10^3 Thus there is good evidence that the infective agent has multiplied in culture A new culture from an entirely different nasal washing has shown the ability to multiply also and the 4th serial culture has produced a cold

Propagation of the common cold virus in culture will give results of little practical value as long as growth of the virus can be proved only by tests on volunteers It is hoped to demonstrate the virus in other ways Cytopathogenic effects on cultures have not been seen but mo t observations have hitherto been of roller tube cultures with low power objectives Various methods of microscopy electron microscopy and microbiologic technics have not yet been applied to the problem With demonstration of viral activity in cultures by any of these methods study of the common cold would enter a new phase

[This is encou aging but certainly not yet in a stage where real prog es can be made in study of the common cold virus The work described in the next two articles shows more promise of workability f om the standpoint of d agnostic and epidemiologic investigation —Ed.]

Recovery of New Agent from Patients with Acute Respiratory Illness M R Hilleman and Jacqueline H Werner[8] studied an epidemic of acute respiratory illness among the service personnel at Fort Leonard Wood Mo during the winter of 1952 53 In about 20% of the noninfluenzal cases

(8 P oc Soc E pe B l & Med 85 183 188 J n ry 1954

of varicella encephalitis cases the prognosis should be guarded

[Adults with varicella may seem very ill for a few days chief com plaints being headache and myalgia along the spine Because the rash is so characteristic cerebrospinal fluid examination is seldom done Hence we may not yet know the true incidence of meningoencephalitis in varicella —Ed]

ETIOLOGY OF COMMON RESPIRATORY DISEASE

Propagation of Common Cold Virus in Tissue Cultures. In January 1952 the Common Cold Research Unit[7] (Harvard Hosp Salisbury England) using particularly the roller tube culture technic began an intensive attempt to cultivate the common cold virus in human tissues It had previously been demonstrated that the virus would survive for a time in cultures of embryonic human tissues

Experimental materials were tested for presence of com mon cold virus by intranasal instillation in groups of volun teers In roller tube cultures of adult nasal tissue survival of virus could not be demonstrated though the growth of tissue explants were satisfactory Such cultures formed an inhibitor active in the hemagglutination inhibition test against influ enza viruses Subsequent cultivation of the virus in embryonic human lung was almost fruitless but more encouraging results followed changes in tissue culture technic and the testing of materials from higher passage levels

METHOD —Cultures of human lung tissue were prepared from embryos up to age 16 weeks obtained through termination of preg nancies for medical reasons Five tissue explants were placed in each plasma lined tube to which 1 ml nutrient fluid was added A series of passages was initiated by inoculation of unfiltered nasal washings from a person (D C) with a typical afebrile cold into roller tube cultures The washing was diluted 1 5 in the medium before inoculation and all cultures used for passages were at least 3 days old Several passages in cultures derived from a single embryo were commonly made and at each passage cultures were incubated for three to four days and stored at —76 C until tested in groups of six to nine volunteers Anaerobic and aerobic tests for bacterial sterility were carried out bovine materials were checked for Q fever Tests for influenza and related hemagglutinating viruses were negative

The D C culture materials have produced colds in 13 of

(7) La cet 2 546 547 Sept. 12 1953

proved aseptic lymphochoriomeningitis mumps meningitis herpes meningitis infectious mononucleosis and varicella also failed to show increase in neutralizing antibody for RI-67 agent in the convalescent specimen

It appears that the RI-67 virus recovered from a patient with primary atypical pneumonia at Fort Leonard Wood is unrelated to the agents which cause Q fever psittacosis and influenza The possible relationship of RI-67 to any of the various infectious agents recovered during the past decade from animals eggs or tissue cultures inoculated with materials from patients with common cold or primary atypical pneumonia remains to be determined

The consistent occurrence of an increase in antibody titer against RI 67 in convalescent serums from patients with primary atypical pneumonia and acute respiratory disease in the epidemic suggests that the new agent may be of etiologic significance at least in certain outbreaks of these diseases

[Here we seem to have a major achievement in the long discouraging attack on the problem of common respiratory disease Using tissue culture technics devised by Enders and his associates these workers have isolated a virus responsible for certain cases of primary atypical (viral) pneumonia It is reasonable to expect that additional members of this important group of agents will soon be identified —Ed.]

Isolation of Cytopathogenic Agent from Human Adenoids Undergoing Spontaneous Degeneration in Tissue Culture Wallace P Rowe Robert J Huebner Loretta K Gilmore Robert H Parrott and Thomas G Ward[9] using the chicken plasma clot technic studied cultures of adenoid tissue the adenoids having been obtained during the winter and spring of 1952 53 from young children

During the first week in most cultures there were sheets of epithelium often ciliated with a few areas of fibroblastic outgrowth After 8 28 days in culture 33 of the 53 (62%) adenoids observed for this period demonstrated a characteristic rounding of the peripheral epithelium which progressed to complete destruction of the epithelium within 7 10 days Culture fluids showing this degeneration were transferred to fresh cultures of adenoids human embryonic tissue or HeLa cells and in 13 instances characteristic changes were produced in the recipient cultures Other strains of the agent were carried without difficulty through serial passages and consist

(9) P oc Soc E pe B l & M d 84 570 573 Dec mb 1953

clinical and x ray findings were consistent with a diagnosis of primary atypical pneumonia

Throat washings (collected in veal infusion broth and stored frozen at — 70 C) from a patient with primary atypical pneumonia were centrifuged briefly to remove gross particles and then inoculated into roller tube cultures of adult human tracheal epithelium prepared by the general method of Enders A cytopathogenic agent (RI 67) was recovered in first passage and this organism was readily propagated in HeLa cells following three additional passages in tracheal cultures All further isolations were attempted by direct inoculation into HeLa culture medium

Four cytopathogenic agents (in addition to the agent from the aforementioned patient which was reisolated directly in HeLa culture) were recovered from two patients with primary atypical pneumonia and from two others with acute respiratory disease These agents appeared essentially identical biologically except for a minor antigenic heterogeneity detectable in neutralization tests with serums from patients convalescent from the disease

Neutralization and complement fixation tests were performed with the serums from a representative group of patients in the epidemic and the RI-67 agent The serum of 12 of 14 persons with primary atypical pneumonia or acute respiratory disease reacted positively to neutralization tests for RI 67 agent and that of 13 was positive on complement fixation no patient with influenza had positive reactions

The serums which showed positive results with RI 67 agent were negative when tested for influenza A B and C and for cold and streptococcus MG agglutinins Likewise none of the serums tested showed complement fixation antibodies for Q fever or psittacosis lymphogranuloma venereum group antigen

Neutralization tests performed with RI 67 agent and paired serums from proved cases of human influenza A influenza B psittacosis pigeon ornithosis and Q fever failed to show a rise in antibody titer for RI 67 Similarly negative results were obtained with the paired serums from patients with common cold and with primary atypical pneumonia which showed a significant increase in cold or streptococcus MG agglutinin Specimens from patients with serologically

VIRAL PNEUMONIA

Chemotherapy of Primary Atypical Pneumonia is discussed by Gordon Meiklejohn William G Thalman Daniel J Wahgora C Henry Kempe and Edwin H Lennette[1] Because adequately controlled studies have been so few and because primary atypical pneumonia is often of short duration even without chemotherapy there has been considerable reluctance to accept the thesis that the therapeutic effectiveness of chlortetracycline in this disease has been established Therefore when many cases of primary atypical pneumonia occurred at Fort Ord Calif the effectiveness of chlortetracycline was studied and compared with that of chloramphenicol and oxytetracycline Data were collected on 149 patients who were treated with one of these three antibiotics or with penicillin The penicillin treated group was regarded as the control group

The patients were military personnel all males and with a few exceptions in the young adult age group Patients were included only when infiltration was observed in the chest roentgenogram A substantial proportion of those whose illness exceeded 10 days had cold hemagglutinins in significant titer

Chlortetracycline chloramphenicol and oxytetracycline were given orally in doses of 0 5 Gm every six hours total 2 Gm daily Single daily intramuscular injections of 600 000 units of procaine penicillin were given the control group Duration of therapy was in most instances three to five days

Analysis was based on the course of the patient s temperature after treatment was started Two intervals were determined (1) number of hours before oral temperature reached 100 F (2) number of hours before a sustained drop was noted

Comparison of the febrile course in groups of patients who received chlortetracycline chloramphenicol oxytetracycline or penicillin revealed a difference in favor of the first three drugs The difference was not sufficiently sharp to conclude the argument regarding the effectiveness of these three drugs

(1) J A M A 154 553 557 Feb 13 1954

ently reproduced the degeneration in both human embryo skin and HeLa cell cultures

The incubation period of the cytopathogenic effects in human epithelium is usually four to eight days The following tissues showed cytopathogenic effects after infection with the agent human adenoid human embryonic nose pharynx, palate tongue trachea skin muscle and pancreas newborn human prepuce HeLa cells suckling rabbit kidney and trachea suckling hamster trachea lung kidney skin and muscle and chick embryo lung and skin

The agent has not grown on bacteriologic mediums Activity was destroyed by heating at 62 C for 30 minutes the agent was filtrable through a Mandler no 14 candle with some loss in titer No clinically recognizable disease has been produced by the agent inoculated by various routes into embryonated eggs suckling and adult mice suckling hamsters guinea pigs rabbits rhesus monkeys and a chimpanzee

From these data it appears that an unidentified possibly new tissue culture cytopathogenic agent has been isolated repeatedly from human adenoids undergoing spontaneous degeneration in tissue culture The filtrability and the inability to cultivate the agent on bacteriologic mediums and to demonstrate organisms in stained tissue culture preparations indicate that it belongs to the group of viruses or rickettsias It is tentatively proposed that the agent be designated adenoid degeneration agent abbreviated as A D agent The agent is derived from the adenoid tissue rather than from the nutrient mediums This is indicated by the fact that some adenoids and all human embryonic tissues cultivated in the identical mediums and at the same time have not undergone degeneration although they are susceptible to infection with the agent also repeated attempts to isolate the agents from adenoid cultures not demonstrating degeneration have been uniformly unsuccessful Further investigation is in progress to determine the relation of the agent to the adenoids and to study their possible role in human disease particularly upper respiratory infections

[It would appear that this virus found in over half of samples of human adenoid tissues was being carried more or less as part of the normal throat flora It appears to be related to the Hilleman Werner agent described in the preceding article Much will be made of these discoveries in the next couple of years —Ed]

received placebo even numbers aureomycin No other anti biotics or antipyretics or analgesics were administered except in occasional single doses for control of extremely high fever or severe cough headache or chest pain Gastrointestinal irritation was the only sign of aureomycin toxicity and this occurred in less than 10% of all patients

Evaluation of the duration of the major symptom fever of the physical and radiologic signs of disease and of the incidence of progression relapse and marked remission within 48 hours of the initiation of therapy indicated that aureomycin does not influence the course of this disease

Psittacosis *W W G Maclachlan G E Crum R F* Kleinschmidt and P F Wehrle[3] (Univ of Pittsburgh) treated 10 patients with clinical or serologic evidence of psittacosis Striking variation in the clinical picture and toxicity was noted in this small group Young adults seem to have a much milder form than older people

Man 58 very toxic was hospitalized with pneumonia of both lungs Pleural and pericardial rubs were present as were signs of consolidation of the left upper lobe and both lower lobes of the lungs He had pulmonary edema a pulse of 140 plus cyanosis and neck stiffness He died 20 hours after admission on the sixth or seventh day of illness which was three weeks after a parakeet was brought into his home During hospitalization he received 6 000 000 units of penicillin intramuscularly and 2 Gm chlortetracycline intra venously At autopsy a large 500 Gm soft reddish spleen was noted The parakeet was killed and psittacosis virus was grown from speci mens of the bird as well as the patient s lung and spleen

Enlarged spleens were most impressive and helpful signs both pathologically and clinically In the fatal case the spleen was over three times normal weight As a clinical physical finding a palpable spleen has been very unusual in other types of pneumonia Three of the 10 patients had palpable spleens which however did not appear until the end of the first week and were palpable for a few days only

Acute respiratory infection associated with a palpable spleen may be the only sign leading one to suspect psittacosis It is recommended that palpation of the spleen be done daily in all atypical types of pneumonia The enlargement of the spleen is present for only a few days and could therefore be missed Once psittacosis is suspected serologic virus tests are performed

Human contact with an active case carries some danger

(3) Am J M S 226 157 163 A g t 1953

because about half the patients treated with penicillin had a prompt drop in temperature

When temperatures before treatment were in the highest ranges the proportion of persons whose temperatures dropped promptly following initiation of treatment with the three test antibiotics was greater than that observed among patients who were given penicillin Differences were brought out most sharply in patients whose peak temperature was 103 F or more If any or all of these drugs were effective a considerable proportion of patients should meet one or both of the following exacting criteria (1) temperatures should fall to 100 F within 48 hours (2) temperatures should show a sustained drop within 24 hours None of 12 patients treated with penicillin met either of these criteria In contrast both criteria were met by most patients treated with chloramphenicol oxytetracycline and chlortetracycline

This study shows the difficulty of conducting a definitive test in the chemotherapy of primary atypical pneumonia The results provide further evidence that chlortetracycline is effective and suggest that chloramphenicol and oxytetracycline are at least equally effective

[For a contrary result see the next article The reason for these differences in clinical experience may lie in the fact that more than one agent causes the clinical picture of primary atypical pneumonia (see p 73) Some may be affected by chlortetracycline some not—Ed]

Ineffectiveness of Aureomycin in Primary Atypical Pneumonia Controlled Study of 212 Cases was made by Stuart H Walker The patients were admitted to the William Beaumont Army Hospital during a moderate epidemic of this disease at Fort Bliss Tex during the winter and spring of 1951 52 They were chiefly young soldiers in basic training Initial diagnosis was based on the gradually progressive development of fever malaise frontal headache cough and substernal chest pain with or without the concomitant physical or radiologic signs of alveolar pneumonia

Patients were divided into two groups one was treated with aureomycin 0 5 Gm every six hours until temperature was normal for two days or for a minimum of three days and one was treated with yellow aureomycin simulated placebo capsules in the same capsule dosage and for the same duration Selection for treatment was based on the character of the last digit of the hospital register number odd numbered patients

(2) Am J Med. 15 593 60 November 1953

syndrome in which an antigen of cat scratch fever produced strongly positive skin reactions The antigen was obtained from a fluctuant axillary lymph node of a patient with a typical history and findings of cat scratch disease

Boy 11 had a swollen left eye and preauricular and cervical lymphadenitis (Fig 5) Temperature was 101 F A history of close contact with several cats was obtained Agglutination tests against Pasteurella tularensis were negative and culture of conjunctival secretion yielded a growth of diphtheroid bacilli His condition improved after five days of symptomatic treatment An intradermal test with antigen of cat scratch fever four years later gave a positive reaction

It is concluded that Parinaud s oculoglandular syndrome is a manifestation of cat scratch fever differing in that the conjunctiva is the site of primary infection the initial lesion being conjunctivitis with granulation followed by regional lymphadenitis

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POLIOMYELITIS

Viremia in Human Poliomyelitis Efforts to find virus in the blood of patients with poliomyelitis began in 1909 Virus can be isolated from the blood of chimpanzees and cynomolgus monkeys several days after its ingestion and may persist there for as long as five days In cynomolgus monkeys which became paralyzed after feeding viremia occurred relatively early in the incubation period and as long as six days before onset of paralysis Dorothy M Horstmann Robert W McCollum and Anne D Mascola[5] (Yale Univ) attempted to demonstrate viremia in the human infection by studying contacts during an outbreak of the disease in Ohio in 1952

Poliomyelitis virus was isolated from the blood of 6 to 33 persons infected with a type 1 strain Type 1 virus was isolated from the throat swabs of all six and from the five rectal swabs tested These specimens were collected at the same time as the positive blood specimens The clinical circumstances under which viremia was detected included the minor illness the asymptomatic infection and one instance in which the virus was isolated several days before onset of a mild nonparalytic attack Virus was isolated from one blood specimen which also contained type 1 antibodies

This study shows that the minor illness or first phase of

(5) J E pe M d 99 355 369 Ap 1 1954

and human to human cases have been fatal The disease is probably spread by coughing and sputum the virus having been isolated from the latter It is recommended that anti biotics be given though their effects are not completely known

[Splenomegaly in pneumonia does suggest the diagnosis of psittacosis but it must be emphasized that this finding is not present in most cases of psittacosis —Ed]

CAT SCRATCH DISEASE

Cat Scratch Disease and Parinaud s Oculoglandular Syndrome In 1889 Parinaud described cases of oculoglandular fever which started as conjunctivitis with granulations and was associated with enlargement of regional lymph nodes and

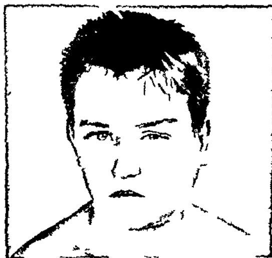


Fig 5—Parinaud s oculoglandular syndrome showing prominent p u ul and e c l lymph 1 op thy (C u t y f Cassady J V and Culbertson C S A M A Arch Ophth 50 68 74 July 1953)

moderate fever which persisted for weeks He believed that the disease was contracted from animals The following have been considered etiologic factors tularemia leptrothrix Koch Weeks bacillus tuberculosis sporotrichosis and lymphogranuloma venereum J V Cassady and Carl S Culbertson[4] (*South Bend Ind*) *present four cases of oculoglandular*

(4) A M A Arch Ophth 50 68 74 July 1953

handling at a national level Hundreds or thousands of injections must be given to provide protection to one or two who may actually profit from it This is blind shotgun prevention in the extreme and has no resemblance to any previous application of passive prophylaxis

Giving injections to all persons in a community simply because the incidence of disease has attained unusual proportions is indiscriminate and wasteful Giving injections to family contacts of diagnosed cases concentrates its use on the most heavily exposed unit of population This avoids also the hazards of epidemic prediction and political pressures and brings some gamma globulin into the communities where blood donations were made The question is Will gamma globulin administered to family contacts be given in time to prevent or modify more cases than if given simultaneously to all children in the community? It would appear wise to extend age coverage in families to include young parents and certainly all pregnant women as there is a tendency for later secondary cases to occur among older children or adults *However since only 1 of 100 or more poliomyelitis infections* are recognized the primary undiagnosed case leads to multiple secondary infections among which may occur one with clinical manifestations With this epidemiologic concept use in the family at the time of exposure of most of the family may be the most effective utilization of gamma globulin

The suspect abortive case contact method is not recommended except where high epidemic rates are recognized Only under these conditions would a high proportion of suspect cases actually represent abortive poliomyelitis infection Under such circumstances treating familial contacts of suspect abortive cases is a more selective method of administration than indiscriminate and essentially mass immunization of all children Not enough gamma globulin is available for all children in all epidemic communities Furthermore 25 50 special teams with tremendous numbers of syringes and needles would be needed simultaneously in late July and August for mass immunization in all heavily hit communities for the procedure differs from that of small subcutaneous injections commonly used in mass immunization A more selective approach to families based on diagnosis or suspect diagnosis by a physician and handled in private practice with

the diphasic cause is a specific infection with poliomyelitis virus and not merely a nonspecific and unrelated disease which precipitates poliomyelitis The relationship of viremia to central nervous system invasion is uncertain The appearance of virus in the blood stream may be vital in the pathogenesis of the disease Draper stated that the biphasic clinical course of poliomyelitis is evidence of a preliminary systemic or *general infection followed by the second* or *central nervous* system phase only when penetration of the blood brain barrier occurred

The findings suggest the following sequence of events as a likely possibility in the human biphasic infection (1) primary multiplication of virus occurring during the first few days after exposure which may be largely or entirely extraneural at this stage (2) development of the minor illness associated with virus in blood throat and feces with viremia persisting only a few days until antibodies appear (3) if the *circulating virus has gained a foothold in the central nervous* system a neural phase of multiplication followed by the characteristic signs of central nervous system involvement

[This excellent combination of clinical epidemiologic and laboratory investigation answers questions which have perplexed students of poliomyelitis for many years —Ed]

Limitations in Use of Gamma Globulin in Poliomyelitis For the first time an agent capable of preventing paralytic disease is available The conditions under which it is effective are definitely limited and not yet completely defined furthermore the agent is in short supply If the recognized limitations of its applications were *better understood by physicians and* the public the enthusiasm about it and demand for it might be less according to William McD Hammond[6] (Univ of Pittsburgh)

Poliomyelitis is a peculiar disease important far beyond its importance It has been dramatized to the point that it carries the psychologic impact formerly reserved for smallpox or bubonic plague Gamma globulin is an immunizing agent that would receive little consideration in any other disease of equal importance in death or disability rates yet it has assumed tremendous importance in poliomyelitis and becomes overnight a $20 000 000 problem requiring emergency

(6) Am. J M Sc 226 125 130 Aug t 1953

Safety of Immune Serum Globulin with Respect to Homologous Serum Hepatitis Immune serum globulin is prepared commercially by two methods (1) salting out e g by means of ammonium sulfate and (2) by the cold ethanol process or a variation of it Minimum requirements of the National Institute of Health for immune serum globulin stipulate that pools consist of at least 500 individuals contributions

Since 1 person among 300 receiving blood transfusions may develop hepatitis Roderick Murray and Frank Ratner[8] (Nat l Inst of Health) suggest that many of the pools of plasma used in the manufacture of immune globulin would be infected with the agent of homologous serum hepatitis The determination of the infectivity of immune serum globulin by inoculation studies in human volunteers was undertaken

A single pool of about 130 L infected plasma was used in all the studies on the safety of plasma and its derivatives Approximately 16 L of this plasma was fractionated by the cold ethanol process The prepared serum was tested for sterility safety and pyrogenicity Two ml of this material was then injected subcutaneously into 10 volunteer subjects and 5 control volunteers each received 1 ml of the original plasma from which the globulin had been produced

None of those receiving globulin had hepatitis but hepatitis with jaundice developed in one of the control group after an incubation period of 84 days Another control subject had positive results of hepatic tests suggestive of hepatitis without jaundice

[The hepatitis virus must remain in fractions other than that which contains immune serum globulin —Ed]

MUMPS

Mumps Skin Test during Mumps Epidemic at West Point N Y was used by Victor J Cabasso (Pearl River N Y) and Robert J Hoagland[9] (M C U S A) in 23 persons involved Despite the limited number of patients different situations that may be encountered by a clinician during a mumps epidemic were presented by the study This epidemic lasted five months and involved 16 males and 7 females aged 2½ 38

(8) P S E p B 1 & M d 83 554 555 J ly 1953
(9) J A M A 15 1527 1530 A g 15 1953

referral of others to health department clinics has much to commend it

[Public interest in gamma globulin has been somewhat diminished as a result of publicity to the mass trial of active immunization with the Salk vaccine It seems pretty certain that gamma globulin has so many difficulties and limitations that not much can be expected of it —Ed]

SERUM HEPATITIS

Incidence of Hepatitis Following Use of Pooled Plasma Follow up Study in 587 Korean Casualties Victor M Sborov Burton Giges and Joseph D Mann[7] state that during and after World War II hepatitis was reported in 2 5 7 3% of recipients of pooled plasma and in less than 1% of recipients of blood alone Both the long incubation type (serum hepatitis) and the short incubation type (epidemic hepatitis) can be transmitted by whole blood or plasma A study was made of *587 Korean casualties who received either pooled plasma or* whole blood during 10 months All casualties were comparable in severity of wound general physical condition and time of evacuation from the theater In most instances the only factor which determined whether a patient received plasma or blood was the local supply situation

Of 255 patients receiving plasma and blood 56 (21 9%) had hepatitis and jaundice Of 332 patients receiving blood alone 12 (3 6%) had hepatitis and jaundice The probable incubation period (from day of injury to first day of jaundice) was 44 151 days mean 90 3 $\pm$ 11 7

Although plasma irradiated with ultraviolet light was used during the latter period of the survey a month by month breakdown of the incidence of hepatitis reflected no significant prevention of hepatitis by irradiation The incidence of hepatitis after whole blood infusion was higher than previously reported and may be due to battle conditions The patient may have received plasma as well as blood which was not recorded in the field medical record or the patient may have received multiple whole blood infusions thus increasing the risk of hepatitis

[These are shockingly high figures and they raise serious question whether plasma should be used in preference to other blood volume expanders such as dextran —Ed.]

(7) A M A Arch. I t. M d 92 678-683 Novembe 1953

days In 194 cases (74%) the illness lasted from one to seven days and in 52 cases from one to two weeks Only 16 persons were ill beyond two weeks and the longest attack was 35 days Generally the illness in children was shorter

Spasmodic pain was practically always present and the character of this constant symptom more than any other factor enabled diagnosis This pain was extremely severe at one time or another in all patients Sudden exacerbations of pain in the abdomen chest and neck and also some frontal headaches were characteristic The usual story was an exacerbation of pain for 5 10 minutes followed by about a half hour of relative relief Usually the patient experienced pain in only one part of the body but in some cases the pain described as stabbing shifted from place to place Slightly more than half the patients reported abdominal pain and about one fifth experienced chest pain

Approximately one third complained of severe frontal headache often likened to a tight band across the forehead A fever of 101 103 F was usual and 40 patients reported vomiting Less common symptoms were photophobia shivering sore throat pain in the limbs or neck dizziness delirium hyperesthesia and paresthesia

Seven patients had proved benign meningitis and in nine others the clinical picture closely resembled that in meningitis This 6% incidence corresponds with series reported earlier Also 3% of the men had orchitis as a late complication Both early and late relapses were characteristic of the epidemic

Viruses pathogenic for mice were isolated from the feces in 6 of 17 cases examined The strain of Coxsackie virus isolated was identified as one of Dalldorf s Group B Paired acute and convalescent serums were obtained from 13 patients and tested for the presence of neutralizing antibody against the Oxford virus A pronounced rise in neutralizing power in the convalescent serum was demonstrated in eight patients whereas the others had a high titer of antibody in both serums

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VACCINIA

Fatal Generalized Vaccinia with Failure of Antibody Production and Absence of Serum Gamma Globulin Smallpox vaccination reactions are generally trivial short lived affairs

Of the group 13 had clinical mumps and the other 10 either had contact with others with mumps or presented postmandibular and preauricular indurations and swellings which were later traced to conditions other than mumps

There are three situations in which the clinician can secure aid from intradermal testing in clinical cases of apparent mumps or in persons exposed to patients with mumps First and probably most valuable is the positive skin reaction in a person whose clinical manifestations closely resemble mumps When a patient with an induration suggestive of mumps behind the ramus of the mandible is skin tested he can be released from isolation within 24 48 hours if the skin reaction is strongly positive thereby indicating immunity to mumps The second advantage is the possibility of diagnosing nonparotid mumps The third advantage is that the clinician can perform skin tests on exposed children who are not sick and if reactions are strongly positive he can tell the parents freely that they need not fear the occurrence of mumps

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BORNHOLM DISEASE (EPIDEMIC PLEURODYNIA)

Oxford Epidemic of Bornholm Disease, 1951 J F Warin J B M Davies F K Sanders and A D Vizoso[1] obtained useful information during an epidemic of Bornholm disease in Oxford England lasting from September to November 1951 Detailed histories were obtained from 262 patients among 277 cases collected undoubtedly many more mild cases remained undiscovered

There were a few sporadic cases in August but the epidemic began abruptly in the 2d week of September The weekly incidence rose rapidly for four weeks and was followed by an equally rapid decline until the 4th week of October The epidemic spread throughout the city but was characterized by local areas of extremely heavy infection The incidence was highest in preschool and young school children The relatively high incidence among young married adults suggested that it is predominantly a disease of young children and their parents but a third of the cases involved single infections in a household

The incubation period ranged from 1 to 18 usually 2 5

(1) Brit M J 1 1345 1351 J 20 1953

should be administered in large doses at frequent intervals If such serum is not available replacement transfusions should be considered

[The suggestion that some of these terrible cases of fatal generalized vaccinia are due to inability to produce antibody is an attractive one —Ed.]

Generalized Vaccinia in Presence of Diffuse Dermatitis Robert J Hall[3] (U S Army Hosp Camp Sendai Japan)



F g 6—M e ed ma g l d (Court y t H II R J U S A med F ce M J 4 1503 1506 Oct b 1953)

states that hematogenous dissemination is suggested by the terminology but the influence of concomitant skin diseases seems to indicate that autoinoculation is more important in the pathogenesis of generalized vaccinia

Man 21 was first vaccinated on Aug 30 1952 with no take In December a pruritic oozing eruption developed in the left axilla by January it had spread to the groin perineum neck and face The eruption was red and scaly with weeping in the intertriginous

(3) U S A m d F M J 4 1503 1506 Oct b 1953

Cases of generalized vaccinia developing over weeks or months following vaccinations though uncommon are usually fatal S E Keiden K McCarthy and J C Haworth[2] (Liver pool) *report a case*

Girl aged 8 weeks was vaccinated and seven days later vesicles appeared around the initial lesion the anus and vulva She was hospitalized three weeks after vaccination with a new lesion on the left hand mild diarrhea and rectal temperature of 99 F Subsequently lesions appeared on other skin areas and the mucous membranes of the nose mouth and probably the larynx Temperature rarely ex ceeded 100 F local reaction was minimal and the spleen and lymph nodes were never enlarged Steady deterioration was evident until death four weeks after admission Coagulase positive Staphylococcus aureus was cultured from the skin lesions and the blood Treatment included penicillin and aureomycin systemically and penicillin pow der tulle gras and gentian violet to the lesions Whole blood from recently vaccinated donors and intramuscular gamma globulin were administered

Pock counts in four eggs each inoculated with 0 4 ml whole blood taken three weeks after vaccination showed that there were more than 50 infective particles/ml in the blood Viremia was present throughout the disease but did show some decrease after administration of serum known to contain neutralizing antibody Vaccinia virus was recovered at autopsy from the bone marrow lymph nodes and skin lesions No neutralizing antibodies for vaccinia virus could be demonstrated in serum obtained before whole blood transfusion and electrophoretic analysis showed complete absence of gamma globulin

Viremia frequently occurs after primary vaccination and this accounts for the widespread nature of generalized vac cinia The course is similar to smallpox and virus neutralizing antibody has been demonstrated However in a few cases widespread lesions continue to appear for several weeks They do not develop normally and fail to heal Noteworthy in this case was the complete absence of gamma globulin for a single specimen of serum In previous work a child unable to form antibodies to a variety of antigens was found to have complete absence of gamma globulin

Treatment of such cases is unsatisfactory but without therapy a fatal outcome is almost certain The use of immune serum from recently vaccinated individuals has been disap pointing and neutralizing activity is not detectable in the serum after nine days It is suggested that hyperimmune serum or convalescent serum from a patient with recent smallpox

(2) A h D Ch ldhood 8 110 116 Ap l 1953

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areas Dandruff was noted for the first time Despite the dermatitis he was revaccinated The eruption became rapidly worse and pruritus increased Six days later he was treated with penicillin but the following day he complained of chilliness malaise and headache The headache became more severe and a red papular rash developed on the face The next day he was admitted to a dispensary with a temperature of 104 F The vaccination site at this time was pustular surrounded by a large area of erythema and edema and beginning to form a superficial crust Temperature elevation persisted and he was transferred to the hospital 12 days after vaccination

He was acutely ill with a rectal temperature of 104 F and a pulse rate of 140 Innumerable pustular encrusted lesions discrete and confluent were present over the face eyelids neck axillae groins genitalia and popliteal areas The eyes could not be opened because of massive edema (Fig 6) Both auditory canals were draining and the right was edematous and occluded The intertriginous areas were macerated and weeping but the corneas were not involved The primary vaccination site on the left arm was covered with a large eschar Generalized vaccinia was diagnosed

The white blood cell count was 14 600 with 82% polymorpho nuclears Antibiotic therapy was instituted Temperatures ranged between 102 and 105 F for the first two hospital days and a low grade fever persisted through the 8th day A diffuse morbilliform rash appeared on the 3d day and faded in two days Within five days edema subsided and almost complete clearing occurred by the 21st hospital day However the underlying seborrheic dermatitis remained in evidence after complete clearing of the vaccinia

Vaccination should not be performed on children with eczema but because of its infrequency little thought is given to the possibility of generalized vaccinia in the military age group Prior vaccination of nearly all adults almost eliminates this problem Routine primary vaccination should not be performed on persons with active skin conditions but revaccination is relatively safe

[Here is another mechanism for the occurrence of generalized vaccinia The lesson about not vaccinating in the presence of an allergic skin eruption needs emphasis —Ed]

HEMORRHAGIC FEVER

Epidemic Hemorrhagic Fever Joseph E Smadel[4] (Walter Reed Army Med Center) states that since the summer of 1951 epidemic hemorrhagic fever has had a considerable impact on medicine in the Far East Command There were approximately 1 000 cases during 1951 and about 700 later

(4) Am J Pub H lth 43 13 7 1330 Octobe 1953

Epidemic hemorrhagic fever encountered in Korea is characterized by a clinical picture of varying severity Onset is sudden with intense headache fever and chills and generally with anorexia and vomiting Temperature rapidly rises to 102 104 F (oral) and stays in this range for four to five days When patients are hospitalized 24-48 hours after onset a definite diagnosis of hemorrhagic fever is difficult or impossible to make

Blood elements are normal except for occasional moderate leukopenia Between the 3d and 4th days a petechial rash appears commonly on the palate and axillary skin folds Transient episodes of hypotension may occur particularly after exertion or periods of extreme restlessness About the 4th day sudden and severe albuminuria develops which is one of the characteristic signs of the disease

The period from the 3d to the 6th day is of particular importance Some patients begin recovery and have an uneventful convalescence In certain of the more seriously affected thrombocytopenia develops with purpura hematemesis gross hematuria and melena In others marked leukocytosis with counts of 20 000 100 000 and a predominance of young cells of the myelocytic series is noted Episodes of hypotension and shock are common during the latter part of the 1st week and probably constitute the greatest hazard to survival Even the severely ill patients are usually out of danger by the 10th or 12th day In those who survive there are rare residuals

None of the specific chemotherapeutic or antibiotic agents has proved of value Most important in the acute illness from the viewpoint of therapy and mortality are hypotension and shock Mortality has varied from time to time and in one group was less than 5% In those who die early the most striking changes are found in the kidney where the medullary tissue is sharply demarcated because of extensive hemorrhages into this region Hemorrhagic manifestations are found in various organs particularly in the pituitary adrenal and right auricle of the heart

Epidemic hemorrhagic fever in Korea is a place disease not a contagious one The epidemic area extends as a belt across the peninsula with the southern border at the level of Seoul the exact northern border being unkown The disease is seeded in sharply defined foci in rural areas and the great

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(4) Am J P b H alth 43 1327 1330 October 1953

*ing ACTH Subjective almost always exceeded objective im*provement Most symptoms returned within the first 10 days after cessation of both cortisone and ACTH therapy and complete relapses occurred within 60 days of cessation of therapy in all but one case Microscopic examination of tissue revealed essentially the same changes with both types of treatment This response consisted principally of a decrease in edema and inflammatory cellular infiltration and some reduction in fixed cellular hypertrophy and hyperplasia

It was necessary to discontinue cortisone therapy in eight patients and ACTH in six because of psychoses considerable fluid retention thrombophlebitis aggravation of diabetes or complicating infections Facial changes including moon facies hirsutism and acne were relatively frequent Edema potassium loss (manifested by weakness and electrocardiographic changes) hypertension aggravation of previously existing diabetes changes in mental status and defective wound healing were noted during therapy Infection developed in six patients receiving cortisone and five receiving ACTH One patient receiving cortisone had a fulminating lobar pneumonia and died within 12 hours of onset of symptoms Two postmenopausal women given cortisone had compression fractures of the lumbar spine

The most satisfactory treatment schedule with cortisone began with 100 150 mg a day with a prompt decrease to 100 mg daily as the rate of improvement diminished After the initial reduction aspirin which had been discontinued shortly before cortisone therapy was begun was resumed in full doses When symptoms became stabilized on 100 mg a day in addition to aspirin the dose of cortisone was again reduced by 12 5 mg every two or three weeks to the lowest maintenance level

Hormone therapy represented but one component of a total therapeutic program conservative measures being employed concurrently Such measures not only enhance the over all therapeutic result of hormone treatment but help to reduce the degree of dependence on it

Although cortisone and ACTH have an ameliorating effect on rheumatoid arthritis persistence of clinical evidence of synovitis and progression as determined by x ray examination indicates that neither agent completely suppresses the disease

est numbers of patients are seen in the late spring early summer and the late fall early winter periods Trombiculid mites are the most likely vectors

Japanese and Russian workers demonstrated that the disease can be transmitted from man to man by inoculation of body fluids obtained during the first few days of the febrile illness moreover they showed that the agent was filtrable The many lines of investigation hinge on the theoretically simple procedure of finding a suitable laboratory host for the agent

[This dramatic disease has been studied extensively by many of our foremost authorities Much has been learned about its epidemiology and about the general management of the acute cases but as yet no etiologic agent or specific therapy has been discovered —Ed]

RHEUMATOID ARTHRITIS

Observations on Use of Cortisone and ACTH in Rheumatoid Arthritis Although it is too early to determine the effects of cortisone and ACTH on the ultimate course of rheumatoid arthritis—an unpredictable chronic disease—cumulative experience permits certain general conclusions regarding their ameliorative properties William S Clark Henrick O Tonning J Peter Kulka and Walter Bauer[5] (Harvard Med School) report observations on the use of these hormones in 52 patients (28 males) aged 2½ 62 and impressions concerning their possible place in the armamentarium against this disease

Four males had spondylitis with involvement of only the hip or the shoulder or both the other patients had peripheral joint disease Thirty four received cortisone and 10 ACTH alone 8 were given both hormones but on separate occasions Total duration of disease including previous attacks ranged from 1 to 29 years On the basis of criteria approved by the American Rheumatism Association stages II III and IV of the disease were represented

Cortisone induced major subjective improvement in 31 of the 42 patients (74%) and major objective improvement in 16 (38%) Major subjective improvement occurred in 11 (60%) and major objective improvement in 4 patients (22%) receiv

(5) N w E gl d J Med 249 635 64 Oct 15 1953

and nearly all eagerly return for injections when the beneficial effect had worn off Some have gone many months without need for further local therapy

Follow up on the first 547 patients revealed that 106 (20%) obtained lasting relief from symptoms and signs of local inflammation for at least a year since last treated In 296 (54%) relief was temporary but repeated injections successfully maintained relief for more than a year

Adverse effects from injections have been rare and mild Only 2 3% of the 8 693 injections were followed by some untoward reaction Most reactions consisted of a temporary exacerbation of the joint inflammation which persisted from a few hours to several days often with subsequent improvement over the pretreatment state No cause for such an occurrence has been found and seldom has it developed more than once in a given patient Such exacerbations do not contraindicate further injections

This therapy is strictly for local palliation and is not a substitute for systemic therapy in any generalized rheumatic process Supportive therapy should not be neglected when this adjunct is used Intra articular injection of hydrocortisone has proved a useful adjunct to general measures in the management of rheumatoid arthritis osteoarthritis and gout For localized conditions such as bursitis traumatic arthritis tennis elbow and tenosynovitis (e g trigger finger) hydrocortisone injections have been successfully used alone

Local hydrocortisone injections can be used when contraindications to systemic cortisone therapy exist The only contraindications to injection are the presence of infection in or near the joint or disease so widespread that local therapy is impractical Arthritis of spinal joints is not amenable to this form of therapy for anatomic reasons

Systemic Lesions of Malignant Rheumatoid Arthritis Margaret Bevans Judith Nadell Felix Demartini and Charles Ragan[7] (Columbia Univ) describe two patients whose fulminating fatal active rheumatoid arthritis was characterized by pleurisy and pericarditis During cortisone therapy both had osteoporosis with fractures severe and progressive synovitis and finally overwhelming breakdown of the integument Episcleritis noted in both during the deterioration episode

(7) Am J Med 16 197 211 F b y 1954

Complete objective remissions were not observed The drugs are therefore only repressive and their use in this disease can be evaluated only in terms of the degree of improvement obtainable without serious complications of hypercorticism

Because of the rapidity with which relapse occurs on cessation of drug administration the authors are skeptical of the advantages of short term therapy Slight improvement in muscle strength and co ordination may be achieved from exercise programs during short term treatment However it is possible that these gains may be accomplished without the hormone if proper encouragement is given Although relapse can occur with equal rapidity after long term therapy partial suppression of the disease may make possible substantial gains in terms of comfort activity and even rehabilitation

[We have now had enough time and experience so that reliable evaluation of ACTH and cortisone in rheumatoid arthritis such as this are available —Ed]

Intra articular Hydrocortisone in Treatment of Arthritis Joseph L Hollander[6] (Univ of Pennsylvania Hosp) reports results with 8 693 injections of hydrocortisone into the inflamed joints bursae or tendon sheaths of 852 patients Ordinary aseptic precautions without drapes or rubber gloves have been used Local anesthesia was seldom necessary once the operator became familiar with the technic for aspirating each specific joint The aspirating needle could be inserted relatively painlessly into the synovial cavity of the knee ankle wrist hip or other joint that was the major site of *arthritis* The dose of 25 *mg* hydrocortisone suspension was injected without force after excess synovial fluid had been aspirated To be effective locally hydrocortisone must be injected into the synovial space where it can bathe the entire inflamed surface Many of the failures have resulted from improper placement of the suspension near the joint space but not into it

Over 85% of the injections were successful in that they were followed by demonstrable local improvement persisting for three days to many weeks with gradual relapse of the local inflammation to its pretreatment state Successive reinjections have been carried out when symptoms recurred and in one instance a single joint was reinjected as many as 47 times The reaction of patients to this form of therapy has been excellent

(6) A n I t. M d. 39 735 746 O tobe 1953

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Autopsy disclosed necrotic and granulomatous lesions in all stages of evolution and healing in the pleura pericardium myocardium endocardium diaphragm synovia and the kidneys and lungs The primary lesion was fibrinoid necrosis in the walls of small blood vessels Coalescence of several of these injured vessels and the inflammatory response resulted in a lesion indistiguishable from rheumatic nodules

Autopsy has disclosed a high incidence of cardiac lesions in rheumatoid arthritis despite no history of acute attacks of rheumatic fever It is postulated that the two patients had a malignant form of rheumatoid arthritis which is a systemic disease with cardiac involvement of the heart It differs morphologically from rheumatic fever in the granulomatous character of its valvular myocardial lesion and absence of Aschoff bodies After healing of milder forms of the disease the resultant valvular deformities hitherto attributed to rheumatic fever would account for all but the few coincidental and documented cases of acute rheumatic fever that are likely to occur in any large series of rheumatoid arthritis cases Long term cortisone therapy apparently does not prevent development of this form of rheumatoid disease

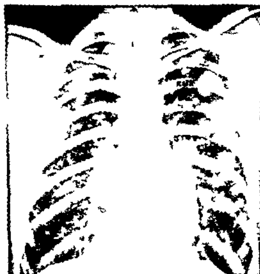
[This so called malignant type of rheumatoid arthritis seems to stand somewhere between that disease and disseminated lupus erythematosus in the spectrum of the collagen diseases —Ed]

Epidemiologic Study of Rheumatoid Arthritis Associated with Characteristic Chest X ray Appearances in Coal Workers W E Miall Anthony Caplan A L Cochrane G S Kilpatrick and P D Oldham[8] studied coal miners in South Wales to investigate this new syndrome described first by Caplan in 1953 The pulmonary lesions associated with rheumatoid arthritis consist of a nodular fibrosis which is radiologically similar to but distinguishable from the massive fibrosis in complicated pneumoconiosis Numerous discrete rounded opacities scattered diffusely throughout both lung fields develop rapidly They seem to appear in crops Over a few months they attain a diameter of 1 2 cm occasionally as large as 5 cm and thereafter as a general rule they change rela

(8) B r M J 2 1231 1236 Dec 5 1953

tively little over a period of years They may gradually en large and cavitation may occur in them occasionally they contract to form stellate scars or they may calcify Typical rheumatoid lung lesions in a coal miner 40 with a history of rheumatoid arthritis for 11 years are shown in Figure 7

Twenty patients with rheumatoid lung lesions and 60 con trols with progressive massive fibrosis or clinically significant tuberculosis were examined clinically In the study group 55%



F g 7—Typ l mpl f h m t d l g l s l w k w th rheumat d rth t s (Cou t y f M II W E ct l B t M J 1231 1 36 Dec. 5 1953)

had proved rheumatoid arthritis whereas only 3% of the controls were affected No rheumatoid arthritis was found in two similar groups of miners with and without simple pneu moconiosis Clinical examination x ray appearances of pe ripheral joints erythrocyte sedimentation rate and differential agglutination test all indicated that the type of arthritis in these miners differs in no way from rheumatoid arthritis in other people There was no close relation between the more typical rheumatoid chest x ray findings and the activity severity and time of onset of arthritis or between the chest

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ment in the precortisone group 21 (46%) were left with residual involvement as compared with 54% in the cortisone group The similarity of the incidence of heart disease is sur prising in view of the well being of the patients and the marked clinical improvement in some children with acute carditis during cortisone therapy If cortisone as used in this series would reduce the occurrence of rheumatic heart disease this fact should have become apparent

Periarteritis Nodosa Report of Case of Apparent Recov ery in a Nine Year Old during Cortisone Therapy is presented by John H Dent Jack E Strange Wallace Sako and Dorothy J York[1] (Tulane Univ) primarily because of the duration of the disease and the dramatic response to cortisone and appar ent recovery after other therapy had failed

Boy 9 had complained for 2½ years of abdominal discomfort and recurrent muscular and joint pains He had repeatedly had in termittent fever and episodes of dermatitis initially urticarious then hemorrhagic then gradually disappearing in two to three weeks Gangrene of the fingers had appeared from time to time Rash and edema had followed sulfonamide therapy Weakness and weight loss progressed and for 30 months his health gradually declined Three months at bed rest and treatment with sulfonamides streptomycin and penicillin failed to check the decline On hospitalization he was acutely and chronically ill had generalized lymphadenopathy and small ill defined subcutaneous nodules over a protuberant and rigid abdomen Thoracic and abdominal veins were strikingly visible Red blood cells numbered 2 700 000 and white blood cells 19 000 Appar ent initial improvement after symptomatic therapy was followed by a recurrence of symptoms Oral temperature rose to 102 F and in durated erythematous areas appeared on the body and extremities Biopsy of an abdominal lesion in the 132d week of illness disclosed classic vascular lesions of periarteritis nodosa.

He was given 100 mg cortisone intramuscularly twice within eight hours 5 gr acetylsalicylic acid was given every three hours to a total of 20 gr during the day Within four hours of the institution of cortisone therapy the temperature had dropped to 98 0 F and the generalized pain had begun to diminish Six hours later the temperature had risen to 101 F but he was more comfortable and could flex his joints without pain for the first time in approximately two years Cortisone and acetylsalicylic acid were continued and on the 3d day although he could not straighten his knees completely he took a few steps for the first time in four months His general condition improved The urine was free from albumin and by the 7th day he was receiving 25 mg cortisone twice daily Moon shaped facies were first noted on the 10th day but he was then afebrile and

(1) A M A Am J D Ch ld 85 556 565 M y 1953

x rays and radiologic evidence of rheumatoid arthritis in the hands and feet It seems likely that in most cases onset of arthritic symptoms coincides with development of the lung lesions

This study has confirmed the observation that a particular type of appearance in the chest x rays of coal miners is closely associated with the presence of rheumatoid arthritis

[One wonders whether this curious syndrome is seen only in Welsh coal miners or whether we will begin to recognize it in other populations —Ed]

COLLAGEN DISEASE

Effect of Cortisone Therapy on Incidence of Rheumatic Heart Disease Arnold L Johnson and Charlotte Ferencz[9] (Children s Memorial Hosp Montreal) compared the incidence of rheumatic heart disease in 100 patients treated with cortisone (a few with ACTH) with that in 80 similar patients treated before cortisone was used In all cases established diagnostic criteria for active rheumatic fever were fulfilled A fairly uniform schedule of therapy was followed

Cortisone was given intramuscularly to 56 patients Usually 200 mg was administered for 2 days and 100 150 mg daily thereafter for 21 days Ten received the hormone for 31 50 days Cortisone was given orally to 38 patients all but 6 received 200 mg for 2 days and 100 150 mg daily for 28 days and these 6 were treated for 40 84 days Six were given 40 60 mg ACTH intramuscularly for 7-40 days

The precortisone group was selected by the same criteria as the cortisone treated group Management of these patients consisted of bed rest and symptomatic therapy Many received salicylate therapy for joint pain but in only a few instances was this continued more than 7 10 days

There was no significant difference in the two series in the incidence of heart disease after the treatment period In view of the dramatic improvement in the severely ill patients on cortisone the incidence of death was perhaps reduced by the drug A larger study series will be necessary to prove this effect

Of 45 patients with cardiac manifestations during treat

(9) New E gl nd J Med 248 845 847 M y 14 1953

may affect one system and at the same time or years later affect another area Before the LE test was introduced many cases could not be diagnosed because there was no simple way to confirm the diagnosis when several systems were involved The clinical picture of systemic lupus erythematosus may be outlined as follows (1) Signs of catabolism fever weight loss emaciation (2) Connective tissue lesions rheumatoid arthritis subcutaneous nodules pericarditis Libman Sacks syndrome with myocarditis pleurisy polyserositis (3) Vascular lesions sl in central nervous system ocular fundi kidney gastrointestinal tract adenopathy splenomegaly Raynaud s phenomenon hyperpigmentation (4) Hematologic changes leukopenia anemia (usually hemolytic) thrombocytopenia increased circulating anticoagulant false positive serologic reaction for syphilis LE cells

The author reports a series of cases illustrating the pleomorphic nature of the disease Arthritis was the most common presenting symptom and was found initially in 34% In evaluating a patient history of pleurisy and effusion years ago thrombocytopenic purpura pericarditis epilepsy rheumatoid arthritis positive serologic reaction for syphilis or other signs may be part of the pattern of systemic lupus In light of the current illness it may be apparent that former symptoms fit into the pattern of systemic lupus Multiple blood and bone marrow LE tests must be performed to confirm the diagnosis When the medical profession forgets the textbook picture of the disease and realizes it is half as common as acute rheumatic fever and more common than pernicious anemia the disease will be correctly diagnosed The prognosis is good especially when diagnosis is early and hormone therapy is instituted before involvement of the central nervous system and advanced renal damage

[Badly word d title but the author s point is right we are making the diagnosis much more frequently now than formerly thanks to the LE test Not many would agree with his opinion that the prognosis is good even with early diagnosis See the next article —Ed]

Effect of Cortisone and Corticotropin on Prognosis of Systemic Lupus Erythematosus Survey of 83 Patients with Positive Plasma LE Tests is presented by John R Haserick[3] (Cleveland Clinic) This disease was among the first to be treated with cortisone and corticotropin In many cases strik

(3) A.M.A A h D rm t & S h 68 714 7 5 D mb r 1953

free from pain Slight hypertrophy of the breasts was noted on the 16th day but it caused no pain and did not intensify

On the 18th day he had an exacerbation and sudden fever of 104 F On increase of cortisone dosage to 100 mg daily for six days the manifestations subsided and the temperature returned to normal During the 5th and 6th weeks while he was being maintained on 25 mg cortisone/day he was increasingly active A second biopsy disclosed changes interpreted as healing periarteritis of the skin A laparotomy was done on suspicion of appendicitis When cortisone was discontinued on the 55th day a total of 3 025 Gm had been given Vitamin supplementation was continued There were no symptoms of adrenocortical atrophy and he continued to improve

Six days later he was sent home He could stand erect and was able to undress without difficulty He was mentally alert and his emotional attitude was good Follow up six weeks later showed that he was enjoying increasingly good health The moon shaped facies had disappeared and the abdominal incision had completely healed He recovered promptly from a tonsillectomy Reactions to all tests were within normal limits His health was still normal two years later

Cortisone may have served only to suppress reactions that might otherwise have proved fatal thereby providing protection for a time until disease processes abated

Effect of LE Cell Test on Clinical Picture of Systemic Lupus Erythematosus Edmund L Dubois[2] (Univ of Southern California) describes systemic lupus erythematosus as a relatively common disease that has no classic pattern Diagnosis is based on an evaluation of the entire clinical picture with the aid of the LE test Because of its varied forms many of these cases masquerade under other diagnoses

At the Los Angeles County Hospital the disease was diagnosed only 11 times in 1948 49 During the following two years when the LE test was used in an active search for new patients 44 cases were diagnosed Cases are more numerous because the concept of the disease is broader and diagnostic acumen better With the aid of Hargraves test felt to be pathognomonic it is usually possible to confirm a tentative opinion The incidence of lupus was exactly one half that of rheumatic fever

Hargraves test has greatly expanded the concept of lupus by permitting diagnosis of equivocal cases and has spurred biochemical studies which are the key to the etiology The illness is subject to many exacerbations and remissions which

(2) Ann Int Med 38 1265 1 94 June 1953

committed suicide during the sixth week of a corticotropin induced remission Autopsy showed no evidence of systemic lupus erythematosus in any tissue

Not stressed in the statistics as presented is a frequently noted improvement in morbidity One patient who usually had three to four attacks of pneumonitis a year had not been ill during three years of a cortisone induced remission Another patient bedridden for two years before steroid therapy had been working for two years

It is in the subclinical atypical forms of systemic lupus erythematosus that use of steroid therapy is debatable If both the patient and the attending physician can be made aware of the potentialities of the disease it is better to withhold specific therapy until an acute exacerbation occurs On the other hand once steroid therapy is started great caution must be exercised before the drugs are discontinued

Collagen Disease Complicating Malignancy John Lansbury[4] (Temple Univ) reports six cases to call attention to a significant and little recognized relationship between neoplastic disease and the so called collagen group of rheumatic or connective tissue diseases

CASE 1—Man 44 had painful joints for four months Examination disclosed the typical findings of rheumatoid arthritis About a month later he complained of radicular pain arising from a lumbar segment and of dysphagia Subsequent studies revealed a carcinoma of the esophagus with metastases to the lumbar spine and a supraclavicular lymph node

The neoplasm almost certainly preceded the arthritis The diagnosis of rheumatoid arthritis rather than of rheumatic fever seems justified from a clinical viewpoint The rheumatic process appears to be an incident occurring during a rapidly evolving malignant process even though it was at first the outstanding feature

CASE 2—Woman 52 noted generalized muscle pain some months after surgery for a Krukenberg tumor Several months later she had arthritis

This case illustrates the appearance of a low grade rheumatoid arthritis during the course of a fatal malignancy

CASE 3—Man 69 had an erythematous rash of sudden onset on all four extremities face neck and upper thorax Generalized stiffness pain weakness and swelling of the musculature followed in a few days Dermatomyositis was diagnosed Autopsy revealed a papil

(4) Ann. Rh. m. t. D. s. 12 301 303 December 1953

ing benefit has been reported, but despite apparent advances in treatment patients still die of the disease The question is raised of how many live and for how long because of steroid therapy (The term steroids is used to indicate cortisone hy drocortisone acetate and corticotropin) In the 83 personally observed cases the clinical diagnosis was supported by the presence of the Hargraves LE phenomenon as demonstrated by one or more positive plasma LE tests

Because of the short interval between the discovery of plasma LE tests in February 1949 and the use of steroids in the management of systemic lupus erythematosus in Novem ber 1949 only 10 untreated patients with positive LE tests were available for study Average total duration of illness in this group (1948-49) was 2 years 7 months The one control still living is in a complete laboratory and clinical remission five years after her last exacerbation

The first group of patients (15) treated with steroid *(1949 50) and the controls were used to study duration of life with this illness Eleven of the steroid treated group were clas* sified as having imminently fatal lupus erythematosus Seven were alive in 1953 Only 1 of the 10 untreated patients with a similar degree of illness lived longer than one year Thus steroid therapy used without interruption over a long period appears to have prolonged the life of a significant number of patients The dosage used to main ain remissions varied ac cording to the individual requirements of the patients from 10 units of corticotropin to 100 125 mg cortisone acetate daily

The continued lives of 30 (68%) of 44 patients in the steroid treated group who were considered to have imme diately fatal systemic lupus erythematosus were attributed to this therapy Since these patients were still living in 1953 most have survived beyond the one year noted previously in the fatal cases of the control group

Of 14 steroid treated patients who died 4 had progressive renal failure despite therapy A few died in LE crisis identical with that of presteroid days One patient died of septicemia with an unidentified fungus Autopsy revealed abscesses com posed mostly of mycelia in nearly every organ Two patients died from complications commonly considered to be induced by steroid therapy One patient s death followed a perforated peptic ulcer and peritonitis Another had schizophrenia and

time in a lifespan of say 70 years but rather of a rheumatic disease arising spontaneously in the first six months or one year of a malignant neoplastic invasion

The association of dermatomyositis with neoplastic disease has been reported in 29 cases This suggests that dermatomyositis was precipitated by some factor common to neoplasia in general In 10 of the cases dermatomyositis improved on removal of the tumor

Lansbury concludes that there is indisputable evidence for the appearance of certain members of the group of collagen diseases during the evolution of a wide range of otherwise unrelated malignant neoplasms The reversal of the collagen disease after successful removal of the tumors is strong proof that some phase of malignancy bears a causal relationship to the collagen disease Therefore when dermatomyositis or collagen disease occurs in middle age without a recognizable precipitating factor a careful search for malignancy is mandatory

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SARCOIDOSIS

Altered Immunologic Reactions in Sarcoidosis Maurice Sones and Harold L Israel[5] (Philadelphia) cite the widely accepted observation that patients with sarcoidosis rarely manifest tuberculin sensitivity if they do it is of low level and transitory Also it has been assumed but not proved that the hyperergy of sarcoidosis is restricted to tuberculin To ascertain whether this abnormal behavior is limited to the tuberculin reaction the authors conducted the following immunologic studies among 38 patients who had sarcoidosis comparing results with a group of healthy controls (1) prevalence of delayed skin reactions (2) development of delayed skin reactions after immunization (3) development of circulating antibodies after immunization and (4) alterations of histamine and immediate skin reactions (passive transfer studies)

Patients with sarcoidosis reacted significantly less often than the controls to tuberculin pertussis agglutinogen mumps virus and oidiomycin in delayed skin tests With tuberculin positive reactions were obtained in 36 8% of the patients and

(5) A I t M d 40 260 268 F bru y 1954

lary carcinoma of the right renal pelvis with metastases to the peri aortic lymph nodes a small neurilemmoma of the stomach and poly myositis of the skeletal musculature

Although the main clinical feature was dermatomyositis which ran a six months course and was the immediate cause of death it is certain that a carcinoma of the right kidney existed eight weeks after onset of the illness and was probably present well before onset of the dermatomyositis

CASE 4—Man 36 had recurrent episodes of left testicular pain for about one year Six weeks before admission he had had an epi sode of pain and stiffness of the shoulders and hands which persisted and slowly became worse A search for LE cells revealed 12/500 cells counted

The diagnosis based on biopsy was malignant seminoma of the left testis associated with disseminated lupus erythe matosus with articular manifestations Unquestionably the neoplasm preceded the arthritis

CASE 5—Man 63 had pain in the right knee with subsequent involvement of the left knee and both elbows and later diffuse pain in the long bones and muscles most marked in the low back and thighs Examination revealed a supraclavicular lymph node swelling and fluid in the right knee tenderness of both elbows and minimal flexion deformity of the right elbow and knee a large mediastinal mass (probably a bronchogenic carcinoma) which enlarged rapidly (serial x ray studies) and a metastatic adenocarcinoma (lymph node biopsy)

The arthritis was indistinguishable from rheumatoid arthritis The malignancy almost certainly preceded it al though it produced no local symptoms

CASE 6—Man 57 had a grade 3 squamous cell carcinoma of the epiglottis and larynx which was irradiated and excised in October 1952 In March 1953 arthritis of the left shoulder developed and by July both knees and ankles were involved with pain swelling local heat and fluid accumulation Later a search for LE cells revealed 3/500 counted

Here a respiratory tract neoplasm of at least one year s duration was complicated by a slowly progressive large joint arthritis clinically resembling rheumatoid arthritis The pres ence of LE cells raises the question of coexisting lupus ery thematosus disseminatus as the explanation of the arthritis

It may be suggested that since both neoplastic disease and the various collagen or connective tissue disorders are quite prevalent their coexistence in these patients could be attrib uted to chance The chances to be considered however are not those of coincidence of these two types of disease at any

hilar adenopathy were broadly similar to those with sarcoido sis Enlargement of the lymph nodes usually regressed more rapidly than is common in sarcoidosis with lung changes The frequency with which erythema nodosum occurs in hilar adenopathy suggests that there is some relationship between the two conditions both of which are probably an allergic response to a sensitizing toxin Erythema nodosum occurs much more commonly in females and the sex distribution of hilar adenopathy without erythema nodosum is very similar to that of sarcoidosis

Although the cause of bilateral hilar adenopathy is uncer tain evidence suggests that it is the agent responsible for sarcoidosis and that the condition is a milder or abortive form of sarcoidosis The low tuberculin sensitivity found in hilar adenopathy even in the presence of erythema nodosum does not point to tuberculous infection as a cause Recognition that hilar adenopathy is usually caused by sarcoidosis would make the diagnosis of sarcoidosis almost commonplace and alter the previous concept that it is rare

[The view that erythema nodosum is often a manifestation or pre cursor of sarcoidosis i gaining favor This would seem to be an important advance in our knowledge regarding these still poorly understood syn dromes —Ed]

CORTICOTROPIN AND CORTISONE

ACTH in Treatment of Keratoderma Blenorrhagica a rare disease first described by Vidal in 1893 and characterized by dermatitis and arthritis secondary to gonorrhea is discussed by Bruce Shallard and Ben Kanee[7] (Vancouver)

Girl 19 was hospitalized Apr 25 1953 In January 1952 she had begun to have painful swellings of the feet The disease pro gressed until the kin of the feet became wrinkled and so thickened that she could no longer work In late March chills and swollen and painful joints developed and a spotty eruption appeared on the face trunk and extremities She had fever (101 F) and appeared very ill She had many ulcers in the mouth there were small circular plaques waxy and psoriasiform (Fig 8) the skin on the feet had domeshaped conical vesicular like lesions of varying size firm greatly thickened but not fluctuant (Fig 9) There was a large effusion into the left knee

The eruption spread severely involving also the scalp Blood was transfused to combat anemia Cultures from the uterine cervix

(7) Ca ad M A J 68 561 564 J 1953

66 7% of the controls with pertussis 13.2% and 57 0% with mumps virus 29 6% and 80 0% with oidiomycin 51 9% and 80 0% and with trichophytin 18 5% and 26 7%

The usual skin sensitivity failed to appear in sarcoidosis after immunization with pertussis agglutinogen but circulating antibodies appeared in normal titers Agglutinins developed in normal titer after immunization with typhoid vaccine This normal response to immunization indicates that the mechanism for the manufacture of circulating antibodies is intact in sarcoidosis

The responses in sarcoidosis to the passive transfer of ragweed sensitivity and to intradermal injection of histamine indicated that the cutaneous responses to agents producing immediate reactions were normal

The study proves that the immunologic defect in sarcoidosis is limited apparently involving the production or transport of antibodies concerned in delayed skin reactions That defect is not confined to the tuberculin reaction The relative anergy to tuberculin characteristic of sarcoidosis is nonspecific and therefore cannot be construed to support the theory of a tuberculous origin

[This agrees with other studies and is probably the proper interpretation of the low incidence of positive reactions to tuberculin in sarcoidosis i e a defect in the mechanisms involved in delayed type skin reactions —Ed]

Bilateral Hilar Lymphadenopathy Its Association with Erythema Nodosum N Wynn Williams and Gordon F Edwards[6] report on 17 patients with bilateral hilar adenopathy of whom 12 had erythema nodosum and 7 polyarthritis Also observed were 15 patients with presumed sarcoidosis of whom 2 had erythema nodosum and 49 patients with erythema nodosum without hilar adenopathy Of the 17 with hilar adenopathy 11 were females and 14 were over age 30 10 females had erythema nodosum Most of the 17 patients had a low sensitivity to tuberculin The hilar lymph nodes were enlarged for variable periods Of the 15 patients with presumed sarcoidosis 10 were males and most were between ages 30 and 50 Of the 49 with erythema nodosum 40 were females and most were aged 30 or less The tuberculin test indicated a high degree of sensitivity in 26

The age and tuberculin status of the patients with bilateral

(6) Lancet 1 78 281 Feb 6 1954

hilar adenopathy were broadly similar to those with sarcoidosis Enlargement of the lymph nodes usually regressed more rapidly than is common in sarcoidosis with lung changes The frequency with which erythema nodosum occurs in hilar adenopathy suggests that there is some relationship between the two conditions both of which are probably an allergic response to a sensitizing toxin Erythema nodosum occurs much more commonly in females and the sex distribution of hilar adenopathy without erythema nodosum is very similar to that of sarcoidosis

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[The view that erythema nodosum is often a manifestation or precursor of sarcoidosis is gaining favor This would seem to be an important advance in our knowledge regarding these still poorly understood syndromes —Ed]

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(7) Canad M A J 68 561 564 J n 1953





F g 8 (t p) —Hyp k at t d p f m l f k t d m bl no b g a n th fa h l n m d f m

F g 9 (b ttom) —Cl l hyp k t t l n f k tod m ble b g on th t f p d lect —th l

(Co te f Sh ll d B d K n B C n d M A J 68 561 564 J 1953)

showed Neisseriae gonorrheae and the histologic picture was compatible with keratoderma blenorrhagica

She was given 500 000 units of penicillin daily and in a day or two noted some relief from joint pain and a slight increase in joint mobility After six days of this therapy improvement was considered unsatisfactory and she still had some fever The addition of 1 Gm streptomycin daily made little difference On May 29 20 units of corticotropin (ACTH) daily was started by intravenous drip Amelioration was immediate and striking and all symptoms regressed The temperature returned to normal as did the status of the joints the rash faded desquamated and completely cleared leaving only slight pigmentation Treatment with corticotropin was continued for 10 days Penicillin was then withdrawn and on June 20 she was well able to walk the feet were normal and all evidence of arthritis had cleared

The incidence of keratoderma blenorrhagica has been estimated as low as 1 4 000 to 1 7 500 cases of gonorrhea whereas gonorrheal rheumatism occurs in about 1 of 50 cases Psoriasis arthropathica Reiter s syndrome and keratoderma blenorrhagica have been confused whereas some authors consider that keratoderma blenorrhagica is Reiter s syndrome in which the urethritis is specific rather than nonspecific In pathogenesis the consensus favors the functional allergic idea which postulates sensitization of the joints skin and conjunctivas as a result of bacteremia and by repeated deposition of organisms or disintegration products thereof which act as antigens This hypothesis would fit in well with the usual chronicity or longevity of the gonococcic infection in such cases

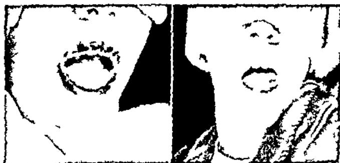
In the case reported the adjuvant contribution of corticotropin would appear to be incontrovertible Undoubtedly the antibiotics are essential to the cure of the neisserian infection but the corticotropin especially if given intravenously by its anti inflammatory or antiphlogistic effect dramatically reduces the morbidity of the otherwise long drawn out and disabling disease

Therapeutic Effect of ACTH in Stevens Johnson Syndrome (Erythema Multiforme Exudativum) is reported on by Ray VanderMeer Doyle E Wilson and Jerry J Bulthuis[8] (Grand Rapids Mich)

Boy 16 was hospitalized Nov 12 1951 with severe sore throat photophobia and bleeding gums The illness started eight days earlier and the day after onset he had a slight cold and sore mouth Small blebs were present between the upper lip and gum and his tempera

(8) N w E gla d J Med 248 806-808 M y 7 1953

ture was 101 F He was given 500 000 units of penicillin and told to use an alkaline mouth wash Two days later the lips were swollen and red the temperature wa 101 F Vincent s organisms were not found and he was given 2 cc of a bismuth preparation and 1 000 000 units of penicillin intramuscularly On November 8 severe con junctivitis and photophobia were present and the temperature was 102 F Eye ear nose and throat consultations were obtained and he was continued on penicillin with Vincent s organisms not being found on repeated examination Hospitalization was suggested be



Fg 10 (ft) —Appe rance f p t t afte fou days of tre tment w th peni cl n and s me chlor mph ol Ulcerat o s on to gue nd l ps h d b c m pro g s v y wo se Pa n had mad at g lm st mpo s ble
Fg 11 (ght) —App a a e of p t ent aft r fou day of ACTH All u e s on l ps had h al d nd there was no l ng r a y bl ding Le ion f the t ngu w re educ d b t st ll present tho gh not p nf l
(Cou t y of Vande M e R t l New Engla d J M d 48 806 808 May 7 1953)

cause of the lack of response to therapy and the severe distress he was having

At admission he was acutely ill and the legs showed six to eight discrete erythematous 1 cm lesions with central bullae The conjunctivas were injected swollen and contained a purulent dis charge Photophobia was severe Ulcers were present on the nasal septum lips and buccal mucosa The temperature was 103 F the pulse 102 and the respirations 24

During the first four hospital days he received large doses of penicillin chloramphenicol benadryl® and ophthalmic ointments The throat and buccal mu osa showed more severe ulceration and the temperature remained at 104 F The conjunctivitis and photophobia increased and the eyelids became markedly edematous Purulent urethritis was noted on the second day with the skin lesions increas ing rapidly By the fifth hospital day his condition was critical and all medications were stopped except 2% yellow oxide of mercury ophthalmic ointment (Fig 10) ACTH 25 mg every 6 hours was instituted and within 12 hours he was able to swallow and chew food No new skin lesions appeared and the old ones regressed Within six hours the temperature dropped to normal and remained

normal Urethritis disappeared within 48 hours but the stomatitis improved more slowly All lesions were considered healed after 4 days of ACTH therapy which was continued for a total of 10 days (Fig 11)

[This disease can be fatal and can lead to blindness ACTH is not always so dramatically effective as described here but is certainly the best treatment we have Because of the possibility of secondary pyogenic infection in the ulcerated and bullous lesions it seems logical to use penicillin or penicillin plus streptomycin concurrently with ACTH (assuming there is no reason to suspect that sensitivity exists to the antibiotics) —Ed]

Studies on Cortisone and Antibiotics for Prompt Therapeutic Control of Typhoid Fever and Scrub Typhus were made by C L Wisseman Jr P Y Paterson J E Smadel F H Diercks and H L Ley Jr[9] (Army Med Service Grad School) Chloramphenicol has been shown to control the bacteriologic manifestations of typhoid fever within a matter of hours but fever and other symptoms may not diminish for three or four days Previously the authors found that cortisone either alone or with chloramphenicol promptly relieved subjective and objective acute febrile manifestations of typhoid fever

Typhoid fever patients were given essentially the same course of chloramphenicol and various amounts of cortisone Rapid and dramatic defervescence was observed in all who received large doses of cortisone (250 500 mg a day) The average time required for these patients to become afebrile after receiving the first oral dose of cortisone and antibiotic was six hours Signs and symptoms commonly attributed to toxemia decreased with defervescence Thus a patient who was in a semistuporous febrile state at noon when therapy was begun might be sitting up in bed at 6 00 p m smiling and showing interest in his surroundings

In nine patients who received cortisone for one or two days and in four who were given the hormone for three days fever headache and other manifestations of toxemia reappeared in 18 72 hours after combined therapy was instituted This escape phenomenon was manifest in 6 24 hours after the last scheduled dose of cortisone in the patients treated for one or two days

Results of this study confirm earlier findings that administration of cortisone in the initial phases of chloramphenicol therapy induced within a few hours a rapid and dramatic

(9) J Cl I t 33 264 275 F b y 1954

regression of the clinical manifestations of the febrile toxic state in typhoid fever

The combined experiences of the authors in over 30 patients treated with a cortisone chloramphenicol regimen indicated that it is desirable to shorten the toxic febrile state so far as possible in the critically ill typhoid patient Patient with mild to moderate disease respond satisfactorily to antibiotic therapy alone

The febrile toxic state of the scrub typhus patients was relieved as rapidly by cortisone-chloramphenicol therapy as was the similar state in typhoid fever However since the response of scrub typhus to specific chemotherapy is usually rapid the cortisone effect is primarily of academic interest

Use of ACTH and Cortisone in Conjunction with Antibiotic Therapy in Management of Overwhelming Infections ACTH cortisone and related compounds have an impressive ability to suppress completely or partially the clinical manifestations of a wide variety of diseases many resulting from specific infectious organisms This suppression is definitely not referable to inhibition of growth of the causative organism and appears to be referable to a nonspecific antitoxic action of cortical steroids of the cortisone type

Lawrence W Kinsell Lenore Boling Leon Lewis John W Partridge and John Jahn[1] (Oakland Calif) made studies to answer the questions (1) Is there any legitimate place for use of these hormones in management of patients with severe nontuberculous infectious disease? (2) Is there any place for the use of ACTH and cortisone in treatment of patients with active tuberculosis?

The answer to the first question is yes though it should be emphasized that ACTH and cortisone have no place in the management of the average infectious process The obvious objective in any infection is removal of the causative organism and this is a relatively simple procedure with the potent antibiotics available today In a certain number of patients intensive chemotherapy fails because of early misdiagnosis neglect or constitutional or other factors In such patients ACTH and cortisone in conjunction with intensive antibiotic therapy may significantly reduce mortality and morbidity

(1) Rocky Mountain M J 50 560 562 July 1953

Some of the conditions in which the combination therapy has been effective are generalized peritonitis meningitis severe pneumonia poliomyelitis tetanus and diphtheria Except in those cases of tuberculous meningitis unresponsive to antibiotic therapy alone ACTH and cortisone should be considered contraindicated in the management of or in the presence of active tuberculous infection However it appears that ultimately these hormones will have a limited place in treatment of certain forms of the disease

[I have seen instances of apparent benefit from the toxic effects of very severe infection when cortisone was used as an adjunct to appropriate antibiotic therapy and think we are justified in continuing cautiously along these lines —Ed]

Action of Hydrocortisone in Synovial Inflammation Ralph A Jessar Mary Ann Ganzell and Charles Ragan (New York City) studied the changes in joint fluid following intra articular injection of compound F acetate (hydrocortisone) in an effort to explain its potent anti inflammatory action This particular action does not follow the use of cortisone Seven patients with rheumatoid arthritis were observed before and one to seven days after intra articular injection All showed definite beneficial effects characterized locally by decrease in pain swelling and other inflammatory signs No definite pattern of response was noted in the total fluid protein however in 14 instances there was an appreciable increase in relative viscosity with in 13 a rise in hyaluronic acid concentration Electrophoretic studies reflected the same changes noted by the measure of total protein and hyaluronic acid

The response to compound F was excellent even in patients whose joint fluid revealed no change in hyaluronic acid concentration It was felt that the total protein cannot be regarded as an indication of the synovial inflammatory state The relatively high viscosity of synovial fluid after intra articular injections of hydrocortisone appears to be related to a change in both character and concentration of the hyaluronate present Thus the changes in the joint fluid reflect a trend toward the normal state It is concluded that the site of action of this agent is the synovial tissue where by suppression of inflammation the synovial membrane cells are permitted to secrete a more normal product

(2) J Cl I t 3 480 48 J 19 3

Effect of Cortisone on Fixation and Neutralization of Diphtheria Antitoxin in guinea pigs was studied by Henry Brainerd and Mirra Scaparone[3] (Univ of California) They tried to establish whether or not cortisone diminishes or exaggerates the fatal action of diptheria toxin or prevents its in vivo neutralization by a specific antitoxin It was found that cortisone failed to exert a protective influence against the fatal action of diphtheria toxin in preventing or delaying death after doses of two different magnitudes Diphtheria toxin may be considered prototype exotoxin in that it is highly potent in action is quantitatively neutralized by antitoxin and is heat labile It is believed to be fixed by a nearly inseverable bond at its site of action and can no longer be neutralized by antitoxin after such fixation occurs True exotoxin does not play a part in most infectious diseases The toxic symptoms encountered in pneumococcic pneumonia typhoid fever and tuberculosis probably arise from a variety of causes produced by the host parasite relationship and in many respects differ from the manifestations produced clinically by diphtheria toxin Contrariwise cortisone failed to accelerate the fatal effect of small doses of diphtheria toxin, although it has the apparent ability to enhance invasion of various micro organisms

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ANEMIA IN ACUTE INFECTION

Hemolytic Anemia in Typhoid Fever Report of Six Cases, Together with Effect of Chloramphenicol and ACTH is presented by A J S McFadzean and G H Choa[4] (Univ of Hong Kong) Among 129 consecutive cases of Salmonella typhosa infection 6 cases of hemolytic anemia were encountered an incidence of 4 6% In another reported series the incidence of hemolytic anemia was 5 9% No cases occurred in 47 consecutive cases of enteric fever caused by S paratyphi A, B or C Interest in the anemia of typhoid began when hematologic investigations in British and Italian soldiers with typhoid fever reevaled a small significant number of cases of hemolytic anemia

The six patients two of them females were Chinese and

(3) Antibiot & Chemother 3 693 697 July 1953
(4) Brit M J 2 360 366 Aug 15 1953

aged 19 38 All were hospitalized during the second week of the disease No history of jaundice or anemia was elicited and exposure to toxic substances or history of blood loss was not found Except in one patient with hemoglobinuria the history in no way differed from that of uncomplicated typhoid and only one patient was aware of being jaundiced

In each case S typhosa was isolated An increased reticulocyte count and normoblastic hyperplasia of the bone marrow were present Qualitative feces urobilinogen tests were strongly positive and marked anemia was present in all cases In three instances the red cell fragility was increased and in the other three it was normal The Coombs test result was positive in the four patients so examined In the absence of blood loss this picture suggests hemolysis

Two patients were treated with ACTH and chloramphenicol two with chloramphenicol alone and two received only supportive therapy The antihemolytic response to ACTH administration and improvement in the typhoid state were prompt No hemolytic response to chloramphenicol alone was detected

It is suggested that hemolysis may be related to the reticuloendothelial hyperplasia which occurs in typhoid The administration of ACTH in two cases controlled the hemolytic phenomena and produced prompt improvement in the typhoid state

[This is an interesting observation The occasional occurrence of hemolytic anemia in typhoid might have been overlooked before since anemia due to blood loss is so common in that disease —Ed]

Anemia Associated with Hemophilus Influenzae Meningitis D Joan Schiavone and Sidney D Rubbo[5] in a survey of *1 069 histories of acute meningitis in infants and children* hospitalized at Children s Hospital Melbourne noted that blood transfusions were used extensively in Hemophilus influenzae meningitis This observation led to an investigation of the frequency and severity of anemia in 196 consecutive cases of this disease and in 141 of meningococcic meningitis

The hemoglobin level chosen as the criterion of anemia was 85% of the expected normal after correction for the patient s age 14 5 Gm hemoglobin/100 ml blood being taken as equivalent to 100% hemoglobin With this standard 89 (45%) of the patients with H influenzae meningitis were anemic on

(5) La t 2 696 698 Oct 3 1953

hospital admission or had anemia within seven days This high incidence is probably a conservative estimate as it does not include 14 patients who received blood transfusions or the many patients given oral iron therapy who were not classifiable because hemoglobin estimations were not recorded In contrast the incidence of associated anemia in meningococcic meningitis was 7 8% (11 cases) These differences suggest that anemia of meningitis may be peculiar to H influenzae infection

In 70% of the anemic patients with H influenzae meningitis the anemia was moderate or severe i e the hemoglobin concentration was less than 75% and 65% of the corrected normal values respectively Thus anemia in H influenzae meningitis not only occurs frequently but is also moderately severe

A definite relation exists between the degree of anemia and the severity of H influenzae infection as measured by the cerebrospinal fluid glucose concentration Anemia was present in 57% of all severe infections (cerebrospinal fluid glucose level below 10 mg /100 ml) in 40% of moderate infections and in 30% of mild cases The age and blood group of the patient and administration of type B rabbit antiserum bore no relationship to the anemia

Whether anemia was a predisposing cause or the result of specific infection is not known It was noted that it often developed during the course of the illness and not infrequently the hemoglobin level fell rapidly in 24-48 hours These sudden changes seem to indicate that mechanisms involving intravascular hemolysis are at work during the infection

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MISCELLANEOUS

Egestion of Phagocytized Particles by Leukocytes According to current concepts bacteria ingested by mammalian phagocytes may be killed and digested by the cell they may survive within the cell for prolonged periods with little or no multiplication or they may prolifera e rapidly killing the phagocyte and escaping Armine T Wilson[6] (Alfred I du Pont Inst) describes another type of outcome in which bac

(6) J E per Med 98 305 310 O t ber 1953

teria having been ingested and enclosed in a digestive vacuole by the leukocyte are ejected by the living cell to the outside and in some instances resume multiplication This process was demonstrated by directly observing by phase contrast microscopy suspensions of bacteria mixed with blood The strains used consisted of beta hemolytic streptococcus group A type I and group A type XIV

METHOD—On clean glass slides a small drop of blood obtained directly by finger prick was mixed with a small loopful of heparin solution of such strength as to give a final concentration of approximately 1 10 000 A small loopful of bacterial suspension was added to the blood and the slide immediately transferred to the Leitz pan phot microscope around which an incubator was built so that the preparation could be kept at 37 C during microscopic examination In preparations of this type human and mouse neutrophil cells remain in excellent condition for seven or eight hours unless overgrowth of extracellular bacteria occurs

Streptococci were phagocytized by human or mouse leukocytes and usually enclosed in a digestive vacuole Sometimes the vacuole emptied itself discharging the cocci to the outside Whether the egested streptococci multiplied in the extracellular environment appeared to depend on how long they had been in the vacuole The ability of mammalian leukocytes to phagocytize particles and egest them resembles that of amebas paramecia and other protozoa known to egest residues of bacteria algae and other organisms that serve as their source of food It is surprising that this capacity of leukocytes has not previously received attention but a search of the pertinent literature failed to disclose reference to the phenomenon

The observations reported have all been made under the artificial conditions of slide preparation One therefore cannot be certain that egestion also occurs in vivo The observations do indicate that leukocytes possess the ability to egest phagocytized particles as least under the experimental circumstances used and it is not unreasonable to suppose that this process may also occur in inflammatory reactions Although it would be relatively difficult to observe the phenomenon in vivo since prolonged observations of individual cells are necessary such a study should be attempted

Bacterial Content of Human Small Intestine in Disease of Stomach When the human intestinal tract is healthy the small intestine is not colonized by a resident flora and only contains

hospital admission or had anemia within seven days This high incidence is probably a conservative estimate as it does not include 14 patients who received blood transfusions or the many patients given oral iron therapy who were not classifiable because hemoglobin estimations were not recorded In contrast the incidence of associated anemia in meningococcic meningitis was 7 8% (11 cases) These differences suggest that anemia of meningitis may be peculiar to H influenzae infection

In 70% of the anemic patients with H influenzae meningitis the anemia was moderate or severe i e the hemoglobin concentration was less than 75% and 65% of the corrected normal values respectively Thus anemia in H influenzae meningitis not only occurs frequently but is also moderately severe

A definite relation exists between the degree of anemia and the severity of H influenzae infection as measured by the cerebrospinal fluid glucose concentration Anemia was present in 57% of all severe infections (cerebrospinal fluid glucose level below 10 mg /100 ml) in 40% of moderate infections and in 30% of mild cases The age and blood group of the patient and administration of type B rabbit antiserum bore no relationship to the anemia

Whether anemia was a predisposing cause or the result of specific infection is not known It was noted that it often developed during the course of the illness and not infrequently the hemoglobin level fell rapidly in 24-48 hours These sudden changes seem to indicate that mechanisms involving intravascular hemolysis are at work during the infection

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MISCELLANEOUS

Egestion of Phagocytized Particles by Leukocytes According to current concepts bacteria ingested by mammalian phagocytes may be killed and digested by the cell they may survive within the cell for prolonged periods with little or no multiplication or they may proliferate rapidly killing the phagocyte and escaping Armine T Wilson[6] (Alfred I du Pont Inst) describes another type of outcome in which bac

(6) J E p r M d 98 305 310 Oct be 1953

tive distribution in plasma was similar to that in blood Strep tococci were found only in plasma The micrococci from plasma represented a number of species those from albumin comprised a greater percentage of the total but fewer species were represented

All strains associated with reactions and all other gram negative rods grew at blood storage temperatures All pseudo monas grew at the lowest temperatures some did not grow at 37 C and the other grew poorly The temperature range for the gram positive bacteria as a whole was higher A few grew at 10 C the upper limit for blood storage The range in which all cultures grew readily was limited to above 25 C and below 30 C

Although technics to prevent contamination of blood are not recommended here it is emphasized that a select group of nonpathogenic bacteria are of prime importance and that rigid bacteriologic asepsis should be used Surgical asepsis is not bacteriologic asepsis

[It is becoming recognized now that the mo t dangerous kind of blood contamination is with bacteria which grow at icebox temperature and not at incubator temperature since the customary storage in the cold would allow these organisms to proliferate yet th ir presence would not be detected by the usual cultural methods One authority has suggested that a gram stain be made of each bottle of blood just before use to detect gross bacterial contamination Certainly this should be done in the investigation of febrile reactions following transfusion —Ed]

Local Infection with Pasteurella Septica Following a Dog Bite Pasteurellosis is commonly seen in animals and birds but is rarely diagnosed in man Cats and rabbits seem to have been responsible for most human cases and despite the fre quent occurrence of pasteurellae in the saliva of healthy dogs only three cases have been reported in which infection in human beings followed a dog bite D F V Brunsdon and B L Mallett[9] (Guy s Hosp London) report a further case

Boy 9 was bitten by a dog on Sept 10 1952 There was a clean gaping laceration of the skin and subcutaneous tissues 3 in above the right medial malleolus The wound was cleansed and sutured and antitetanic serum 750 units given intramuscularly On Sep tember 16 infection was present with edema and discoloration of the wound edges Penicillin was administered and the sutures were removed The wound failed to heal and a swab taken September 17 yielded a pure growth of Past septica

Sulfadimidine therapy was started orally September 23 and con

(9) B t M J 2 607 S pt 12 1953

a few transient contaminants Judith Cregan E E Dunlop and Nancy J Hayward[7] (Univ of Melbourne) aspirated with a syringe and examined bacteriologically the small intestine contents of 22 patients undergoing surgery for peptic ulcer or gastric carcinoma In seven patients with normal acidity or hyperacidity of the stomach the small bowel was either sterile or contained only transient flora Of seven patients with hypoacidity or achlorhydria of the stomach the small intestine was sterile in four and in three contained resident flora in the upper jejunum which was reduced to transient flora in the midgut region The subnormal acidity of the stomach did not affect the normal ability of the small intestine to prevent multiplication of bacteria in its lumen and to destroy large numbers of bacteria entering it from a heavily contaminated stomach

Apparently advanced disease of the stomach with associated physiologic and anatomic changes does not encourage development of resident bacterial flora in the small intestine It is deduced that the small intestine has an antibacterial mechanism which is independent of the gastric germicidal barrier

Study of Bacteria Implicated in Transfusion Reactions and of Bacteria Isolated from Blood Products was carried out by Margaret Pittman[8] (Nat l Inst of Health) following the appearance of recurring reports of severe and fatal reactions after administration of bacterially contaminated blood Eighteen severe or fatal reactions are recorded

It has been claimed that most reactions are due to nonspecific agents and that contamination of the blood or apparatus by pyrogenic agents is the major cause However study of 13 cultures from some of the bloods implicated in the foregoing transfusion reactions or from an associated product showed 8 pseudomonas none of which were Pseudomonas aeruginosa 2 of Paracolobactrum aerogenoides and 3 of Escherichia freundii

Eighty five other cultures from blood products not associated with reactions were also studied Micrococci predominated in both plasma and albumin other culture showed gram negative rods sporeformers and diphtheroids The rela

(7) Brit M J 2 1248 1251 D 5 1953
(8) J Lab & Clin Med 42 273 288 Aug t 1953

20% were first reached more than two years after the patient was dismissed from the hospital

In 35 (22%) it was later possible to establish the diagnosis of the disease that definitely or probably caused the fever (1) Tuberculosis was diagnosed in six cases one was pleuritis three pulmonary affections one spondylitis with a gravitation abscess and one tuberculosis of the lymph nodes Lung roentgenograms were normal in two cases In two others calcified primary tuberculosis was observed and in two dense well delimited streaklike shadows were seen in the parenchyma (2) Malignant tumor or systemic disease was diagnosed in 11 cases (3) Rheumatic fever was found in three and disseminated lupus erythematosus occurred once (4) Nonspecific infections consisted of four cases of sepsis (two originating from the endocardium) and one each of brain abscess infection following abortion appendical abscess chronic cholecystitis chronic pansinusitis (?) and chronic jejunoileitis (5) Cirrhosis of the liver and (6) adrenal disease were each observed twice Most of these diseases were serious 19 patients died and 7 were chronically and incurably ill

Of 54 patients with fever of less than 10 days duration and without rise in sedimentation rate diagnosis was later established in only 4 In addition there were seven cases of premenstrual temperature rise and one of simulation Of those in which no diagnosis other than fever of undetermined origin could be established many were evidently acute infections

Sixty patients had fever of more than 10 days duration with rise in sedimentation rate Of the 20 in whom diagnosis was made 4 had tuberculosis 6 endocarditis and 2 cirrhosis of the liver In the unexplained cases diagnostic suspicions were more precise than in the other groups The patients were hospitalized during a long period (mean 42 days) and all were thoroughly examined In a number of cases sepsis was suspected but repeated blood cultures proved negative In other cases systemic diseases were suspected without definite confirmation being obtained All of these patients were in normal health at the time of follow up—to the extent that they did not have fever Some still had raised sedimentation rates and many had minor complaints but no cause of fever was found

tinued for five days Temperature rose slightly but the patient re mained well No bony changes were present The wound became dry and granular but would not re epithelize despite sufadimidine therapy Split skin grafting was done and healing was complete 68 days after the bite was sustained Wound swabs taken on two occa sions grew a pure culture of a nonmotile gram negative coccoba cillus identified as Past septica

The isolated strain was found to be similar in its sugar *fermenting reactions and antigenically to strains commonly* found in the saliva of healthy dogs Routine swabbing of dog bites might show that infection with Past septica occurs more commonly than is generally realized

Fever of Unknown Origin With Some Remarks on Normal Temperature in Man According to L E Bottiger[1] (Karo linska Hosp) despite increased knowledge and improved diagnostic technic at times fever cannot be explained and the unsatisfactory diagnosis—fever of unkown origin—must be made Many types of fever are covered by this diagnosis Both high fever of long duration accompanied by raised sedimen tation rate and frequently by other atypical signs of severe disease and high fever of short duration in which the entire disease picture appears to be benign are observed In addition there are patients with intermittent fever peaks sometimes over a period of several years Finally there is a large group with low fever which may be most nearly characterized as subfebrility

Horvath and Piersol stated in 1950 that no single normal temperature value exists for all persons nor is there any single normal range of temperature The mean temperature in women not only is higher but shows greater variations than in men Both men and women have a significantly higher temperature in the evening than in the morning

Hamman and Wainwright concluded that 40% of patients with prolonged low fever gradually develop typical symptoms which permit a definite diagnosis 50% recover without diag nosis being established and 10% continue to be febrile without diagnosis

The author investigated patients with fever of undeter mined origin who were hospitalized during 1940 1949 There were 60 men and 98 women but no characteristic age distribu tion Of diagnoses established at follow up approximately

(1) A ta med s a d 147 133 148 1953

The Chest

CARL MUSCHENHEIM M D

Winter Vomiting Disease John F Goodall reports that during the first three months of 1953 he saw 46 patients whose main complaint was sudden and severe vomiting Most of them were under age 40 and onset of vomiting was usually between midnight and 8 a m Onset was preceded by brief nausea accompanied by epigastric pain and some collapse followed by a few loose pale stools Appetite was poor and nausea persisted for a day or two after which recovery was complete Diagnosis of gastric flu was made in many cases but by complement fixation titers to influenza virus A or B in nine patients did not confirm this The disease was not very infectious since 35 patients were the only persons affected in the household Only one patient had a relapse

(2) B t M J 1 197 198 J 23 1954

PART II

THE CHEST

PATHOLOGY

Musculature of Lungs in Chronic Pulmonary Disease Observations on routine sections (obtained from postmortem or surgical specimens) of lung tissue which contained microscopically an unusual amount of muscle led Averill A Liebow William E Loring and Warren L Felton II[1] (Yale Univ)



Fig 1 —B n h l rt y w th m kab pro f at n f l git d nal m s le fiber × 175 Tw l tl k l n s n g ng ppe an f b anch ng S m ny f ba f bow that the p oce s gg t mc n nusu l fo m f canal a on n s l p f obl t t by mu l p l f t Speci m t k f m a m 6 w th h t y f p d t gh f ll w g fl en m 1918 low b t d n 1951 w t f b n h t (Court y of L bow A A t f Am J P th 29 885 911 S pt O t 1953)

to conclude that in many types of chronic pulmonary disease there occur a remarkable hypertrophy and hyperplasia of muscle Much of this muscle is derived from several identifiable sources (1) bronchi and more distal air spaces (2)

(1) Am J P th 29 885 911 S pt O t 1953

lars of muscle and narrow lumens perhaps producin, or contributing an obstructive factor to development of emphy ema Relaxation of this muscle by certain drugs may explain relief from symptoms in certain patients with this condition but further study of its responses is required

The fundamental mechanisms responsible for the muscle hypertrophy and hyperplasia are not fully understood One element may be the effect of entrapment of these fibers at in creased tensions especially in tissue which is undergoing fibrosis

Necrotizing Granulomatosis and Angiitis of Lungs with Massive Splenic Necrosis and Focal Thrombotic Granuloma tous Glomerulonephritis Robert Fienberg (V A Hosp Boston) reports on two patients

Case 1—Man 27 was hospitalized because of hemoptysi weight loss and pain in the left chest A left lower lobectomy for a massive necrotizing granulomatous lesion was performed This was unaccompanied at the time by involvement of other organs Several weeks later he was hospitalized again and died two months later

Ca e 2—Man 54 complained of fever cough and shortne s of breath of four weeks duration He had occasional joint pains There was no history of allergic disorders Urine specific gravity 1 010 1 105 contained 1 to 3 + albumin the sediment contained 50 80 red blood cells in a high power field and many granular casts The white blood cell count varied from 10 700 to 35 300 with 1 3% eosinophils The blood nonprotein nitrogen varied from 74 mg initially to 154 mg /100 ml two days b fore death Chest roentgenograms revealed a diffuse bilateral confluent miliary type of pulmonary infiltration which fanned out from both hilar regions and exhibited greatest concentration in the midlung fields He died nine days later

The terminal course in the two cases was similar and at autopsy the lungs contained well circumscribed often sub pleural lesions similar to those observed in the resected pul monary lobe In addition massive splenic necrosis and focal thrombotic granulomatous glomerulonephritis were noted

Necrotizing granulomatosis with angiitis is believed to be related to but not identical with periarteritis nodosa The presence of a hypersensitivity phenomenon is probable sul

( ) Am J Cl P th 23 413 428 M y 1953

blood vessels especially the longitudinal layer of the bronchial arteries (3) lymphatics and (4) interstitial tissue not clearly associated with other structures Muscle fibers from these sources may become commingled

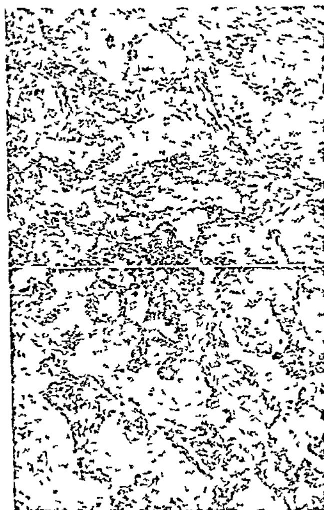
In vessels the lumen may become completely obliterated as a result of muscle hyperplasia thus abolishing a useless or even burdensome collateral circulation (Fig 12)

Hyperplasia of muscle is especially striking in some in



F g 13—Wall f mphy m tous from p ph y of lu g t f b ll ha ge d d f m × 35 B lk f h nt bullou pt m ou t of m s l t th t ha b m hyal n d n f w pl c nly Sp cim n tak n f m m 54 w th fi y a h to y f h tn f b th Spo t n p m th o cur d ju t b f p at n fo c n of b ll (Cou te y of L bow A A *et al* Am J P th 29 885 911 S pt Oct 1953)

stances of pulmonary emphysema the walls of the bullae containing masses of myoid tissue derived from all of the sources mentioned previously (Fig 13) Compaction of the residual tissue occurring concurrently with the destructive process responsible for development of the bullae in part accounts for the abundance of muscle in the walls The bronchioles leading to the emphysematous region may possess great col



F g 14 (top) —D m nated t z g g a l m tos d g t S g lly sec ed l w h lf f l ft l g N m ou cu l t d m ph ges fill d w th S da IV po t h l t l h l p d l m f l l C mpa w th F gu 15 H m t yl eo × 125

F g 15 (bott m) —Comb d g p P m t f th h l t rol type. N m ou acu l d m phag fill d w th S d IV pos t h l l h l p d in l men f l l d th k d l eol w ll C mp w th F gu 14 Hemat yl eos × 125

(Court sy f F enbe g R Am J P h 29 913 931 S pt Oct 1953)

fonamides are the most likely sensitizing agents However they are not the only probable sensitizing agents since identical cases were reported before their introduction

[Fienberg has found similar cases published under the diagnoses periarteritis nodosa allergic granuloma, giant cell granuloma granuloma with periarteritis nodosa eosinophilic granuloma rhinogenous granuloma, Wegener s granuloma lupus erythematosus rheumatic or pararheumatic disorders Loeffler s syndrome and granulomatous glomerulonephritis He regards the type of tissue reaction as different from classic periarteritis nodosa as was also recognized by Wegener The eponym Wegeners granulomatosis is rejected because priority belongs to Klinger who first described cases of this type but regarded them as a type of periarteritis nodosa In the following article Fienberg compares the two cases here described with cases of chronic pneumonitis of the cholesterol type so diagnosed on surgical resection —Ed]

Necrotizing Granulomatosis and Angiitis of Lungs and Its Relationship to Chronic Pneumonitis of Cholesterol Type Robert Fienberg[3] (Harvard Med School) compares six cases of chronic pneumonitis of the cholesterol type and one case of idiopneumonic necrotizing granulomatosis and angiitis with two cases of disseminated necrotizing granulomatosis and angiitis (Fig 14) In all cases lung lesions often in the form of subpleural masses included ulceration and obstruction of the bronchioles and small bronchi fibroblastic proliferation collagen deposits and vacuolated macrophages filled with cholesterol rich lipid The idiopneumonic necrotizing granulomatosis appeared to be a transition between the chronic pneumonitis of the cholesterol type (Fig 15) and the disseminated necrotizing granulomatosis and angiitis

The hypothesis is offered that the primary disorder in pneumonitis of the cholesterol type is the ulceration and obstruction of the smaller branches of the bronchial tree which bring about the appearance of intra alveolar macrophages filled with cholesterol rich lipid the latter being a secondary phenomenon These changes in the small branches of the bronchial tree may be caused by a hypersensitivity phenomenon similar to but of lower intensity than that responsible for like changes in both idiopneumonic and disseminated necrotizing granulomatosis and angiitis This may represent an Arthus reaction localized in the bronchial tree Cause of the sensitization is unknown

(3) Am. J Path. 29 913 931 Sept O t 195;

is true of systemic conditions directly involving the mediastinal nodes The simple scalene node biopsy is thus a biopsy of the mediastinal nodes without entering the thorax The percentage of positive findings in the nodes varies with the pathologic conditions and the accuracy of the dissections In 67 of 187 patients Lawrence M Shefts Arthur A Terrill and Herbert Swindell[5] obtained convincing evidence of the identity of associated intrathoracic disease which was previously undiagnosed (Tables 1 and 2)

Scalene node biopsy is of value in all cases of proved bronchogenic carcinoma for determining extent of metastasis

TABLE 1—INCIDENCE OF ABNORMAL FINDINGS AMONG 187 PATIENTS WITH PREVIOUSLY UNDIAGNOSED INTRATHORACIC DISEASE

Total series 187 patients	203 biopsies (17 bilateral)
Number with abnormal scalene nodes	67 patients
Percentage of positive findings	35 8

TABLE 2—PREVIOUSLY UNDIAGNOSED INTRATHORACIC DISEASE

Diseases			Patients
Abnormal nodes			67
Disease of nodes			
Boeck s sarcoid			38
Bronchogenic carcinoma			13
Undifferentiated	9		
Adenocarcinoma	4		
Tuberculosis			8
Lymphosarcoma			2
Hodgkin s disease			2
Histoplasmosis			1
Metastases of tumor to the lung			3
Carcinoma of pancreas		1	
Hypernephroma		1	
Carcinoma of cervix		1	

Biopsy should be done in all cases of suspected bronchogenic carcinoma When hilar and/or mediastinal enlargement is visualized by x rays biopsy will reveal Boeck s sarcoid enlarged tuberculous mediastinal nodes lymphosarcoma and Hodgkin s disease Cultures from scalene nodes can aid in diagnosis of pulmonary fungous infection The value of isolation of tubercle bacilli from these nodes in the diagnosis of a tuberculous pulmonary parenchymal lesion remains to be proved In cases of pulmonary infiltrates or infiltrations suspected of being metastatic tumors scalene node biopsy material may reveal the exact microscopic type of tumor and

(5) Am Rev Tuberc 68 585 52 Oct be 1953

Usefulness of Hotchkiss-McManus Stain for Diagnosis of Deep Mycoses John H Seabury J Winthrop Peabody Jr and M Jack Liberman[4] (Charity Hosp of Louisiana) consider the periodic acid Schiff stain most useful for demonstration of fungi in tissue The Schiff reagent is prepared by decolorizing basic fuchsin with hydrochloric acid and anhydrous metabisulfite A colorless fuchsin sulfurous acid is formed which will combine with aldehydes When this combination takes place the reagent is recolorized by the addition of aldehyde and if the aldehyde is relatively insoluble the substance containing it will be stained varying shades of pink to red to purple

Hotchkiss and McManus working independently found that periodic acid could be used to oxidize certain carbohydrate mucoproteins and glycoproteins to aldehydes which could then be colored by the Schiff reagent The pathogenic fungi and some bacteria contain material which after oxidation with periodic acid will form colored addition compounds with the Schiff reagent Not only does the staining method reveal fungi with exceptional clarity and detail but the color contrast is striking Organisms appear in varying shades of red and if green is used as a background stain rapid survey of stained sections is possible with the low and high power dry objective

Two cases are presented in which fungi could never be demonstrated by hematoxylin eosin stains but were readily found by the periodic acid Schiff method In two other cases histologic diagnosis was not made until biopsy material was stained with the Schiff reagent and in another case proper identification of the fungi was greatly facilitated by the staining method The fungi identified included candida coccidioides histoplasma and blastomyces

Scalene Node Biopsy The lymph nodes anterior to the scalenus anticus muscle are connected to the mediastinal nodes and pulmonary parenchymal lesions that might involve mediastinal nodes are reflected in the scalene nodes The same

(4) Di Ch st 25 54 69 J i a v 1954

lation in individual countries have been noted Though mostly less dramatic than the differences in countries they made it possible to define more precisely the differences in environment to which the separate groups have been exposed The death rate from lung cancer in 1950 was twice as high among the men of Greater London as among men living in rural districts and the difference was more pronounced in the older age group The rates for other parts of the country fell between the Greater London and rural rates in exact order of town size Comparison of the relative differences at different periods shows that these differences have remained remarkably stable despite the great increase in the recorded mortalities

There is evidence that the development of bronchial car cinoma may be due to prolonged exposure to a number of atmospheric carcinogens Some of these substances such as radon benzpyrene and arsenic are present in town air though in much lower concentrations than in industry others such as nickel are peculiar to specialized industrial processes and others are as yet undetermined None of the occupations known to be associated with a high incidence of lung cancer appears to carry any increased risk of laryngeal cancer

In all reports the incidence of lung cancer is much higher in men than in women The accurate Danish cancer registra tion scheme suggests that the true sex ratio is probably some what though not much higher than that indicated by death certificates and the true ratio in the United Kingdom is prob ably at present of the order of 6 or 7 1 At the beginning of the century the ratio of men to women was as low as 1 3 1 In Norway the ratio to this day is not much greater Generally it would appear that in all countries the higher the incidence of the disease the greater the male preponderance but the rela tion between the sex ratio and the total incidence is not the same in all countries It seems probable therefore that the factor mainly responsible for the increase is one to which men are particularly exposed and that the extent of the rela tive difference in exposure of men and women varies from country to country

The possible relationship between the smoking of tobacco and the development of bronchial carcinoma has often been suggested (table) Men smoke more than women but it is

with clinical findings may lead to the prompt detection of the primary site of the neoplasm In cases of medicolegal interest (pneumoconiosis) the offending foreign body may be identified by scalene node dissection

In 205 biopsies the only complications observed were tearing of the thoracic ducts in three instances and a temporary Horner syndrome in one

[Biopsy of this group of lymph nodes for the diagnosis of mediastinal and pulmonary disease was introduced by Daniels in 1949 The method is gaining wide acceptance because by its use it is frequently possible to avoid more formidable procedures such as exploratory thoracotomy or lung biopsy It should be noted that it is in the *absence* of any palpable cervical or supraclavicular nodes that the scalene node biopsy is indicated. As in other lymph node biopsies much of the value of the procedure is lost if bacteriologic preparations are not always made in addition to histologic sections The usefulness of the Hotchkiss McManus stain (see the preceding article by Seabury and his associates) is noted in this connection —Ed]

NEOPLASMS

Bronchial Carcinoma Incidence and Etiology are discussed by Richard Doll[6] (Med Res Council) How much of the increased incidence of this condition is real after standardization for age and sex is uncertain The change in the last five years when facilities for diagnosis have been readily available suggests that the real increase is likely to be large On the other hand some of the increase is nosologic and some is due to the therapeutic advance which prevents death from pneumonia before presence of the underlying growth is evident This holds out hope for prevention Some potent environmental factor must have become prevalent therefore when the factor is identified it may prove possible to reduce its influence

Real differences in incidence in different parts of the world probably exist even though all of some differences may be nosologic the incidence is particularly high in Britain compared with that in Norway Iceland and some African and Asiatic countries However in all countries which have recorded vital statistics of lung or respiratory cancer the death rate has increased substantially

Important differences in incidence in sections of the popu

(6) B r M J 2 521 527 S pt 5 585 590 S pt 1 1953

mortality from the disease in the United States Animal experiments confirm the carcinogenic potency of tobacco smoke but the active agent has yet to be isolated The position with regard to pollution of the atmosphere with chimney smoke is uncertain The higher mortality in urban areas and the larger towns may perhaps be explicable on the grounds that cigaret smoking has been heavier in these areas on the other hand chimney smoke may be found to exacerbate the effect of the tobacco factor Apart from certain mass radiography statistics the meaning of which is difficult to assess there is no epidemiologic evidence to implicate pollution of the air with the exhaust fumes of cars or with road dust

[This important two-part publication of the author s Milroy Lectures summarizes virtually all the existing knowledge concerning the epidemiology of lung cancer including the controversial subject of the relationship to tobacco consumption The evidence which tends to incriminate tobacco smoking is derived from studies conducted by the *historical method* This is retrospective inasmuch as the data are obtained by questioning lung cancer patients and a control group concerning their past and present smoking habits The next article describes a study by the *follow up method* which has been set up This method appears to be free from certain objections which may be raised against the historical method but the time required to obtain the desired information may be very long The study also has the po sible defect that to make it financially feasible it has been necessary to use a questionnaire and volunteer workers rather than professional interviewers and follow up workers—Ed]

Smoking in Relation to Lung Cancer Follow up Study E Cuyler Hammond[7] (Yale Univ) reports an increase in lung cancer deaths in recent years among males and to lesser extent among females to a point where 21 000 persons die annually of the disease in the United States with annual deaths increasing by about 1 000 Peak death rate among men occurs at ages 65 69 and among women at 75 79 and death rates are higher in urban than in rural areas Among environmental factors possibly responsible for the increase are (1) air pollution from coal and oil furnaces (2) exhaust fumes from automobiles and (3) cigaret smoking

Evidence pointing to cigaret smoking as the causative agent in lung cancer includes (1) time trend (2) results of laboratory tests on animals and (3) history of heavier cigaret smoking among lung cancer patients than among controls According to the time trend evidence the incidence of lung cancer and the rate of cigaret consumption have increased at the same time this evidence however is subject to mislead

(7) C t cut M J 18 3 9 J ry 1954

not evident whether the difference in smoking habits is sufficient to account for the observed sex ratio The mortality rates which have been estimated for different levels of smoking among men and women in London suggest that sex differences still persist at each level Trade statistics show that, although 22% of all tobacco was smoked by women in 1950 the proportion smoked by them 25 years earlier was only 2 5% Consequently there must be a much greater difference in the total amounts smoked by men and women now in the cancer age than is revealed by the histories of their recent

SMOKING HABITS OF MEN WITH AND WITHOUT LUNG CANCER

Author	Date	No with Cancer	No without Cancer	Nonsmokers % With Cancer	Nonsmokers % Without Cancer	Heavy Smokers % With Cancer	Heavy Smokers % Without Cancer
Muller	1939	86	86	3 5	16 3	65 1	36 0
Schairer and Schoniger	1943	93	270	3.2	15 9	51 6	26 7
Wassink	1948	134	100	4 8	19 0	82 0	45 0
Schrek *et al*	1950	82	522	14 6	23 9	18 3†	9 2†
Mills and Porter	1950	444‡	430	7 0‡	31 0	—	—
Levin *et al*	1950	236	481	15 3	21 7	—	—
Wynder and Graham	1950	605§	780	1 3§	14 6	51 2§	19 1
McConnell *et al*	1952	93	186	5 4	6 5	35 0¶	21 5¶
Doll and Hill	1952	1 357	1 357	0 5	4 5	25 0	13 4

D fin t o va s f m o e th t n the
† P c tage of h y g t m k
‡ F g e l t t ll p t y n
§ F gu l t t l ng ca the th d m
¶ P t g m g m n nd wom n (93 m nd 7 w m n a d 186 m d 14 w men spe t vely)

smoking habits The rates calculated for smokers of different average amounts therefore do not seem truly comparable for men and for women Comparison of the incidence among non smokers would seem more correct but is not accurate because of the small numbers involved nevertheless the similar incidence among men and women is striking and it seems probable that save for smoking and exposure to certain industrial risks the disease may affect men and women equally

In summary most of the known epidemiologic facts about bronchial carcinoma are consistent with the effects of a limited number of industrial carcinogens and the presence of a carcinogenic substance in tobacco smoke particularly in that derived from cigarets An exception may be the relatively low

ning of the influence of the carcinogenic effect to the death of the patient

The carcinogenic influence in Copenhagen must therefore have begun to exert almost full effect about 1900 1910 Even if it is assumed that the carcinogenic influence to which the cohort 1905 was exposed represents the maximum possible and that the age distribution for men in Copenhagen does not change—both of which assumptions may be rather conserva

FUTURE ANNUAL NUMBER OF DEATHS AMONG MEN IN COPENHAGEN

1951 55	241	1971 75	808
1956 60	362	1976 80	919
1961 65	507	1981 85	979
1966-70	660	1986-90	1 007

C mp ted th b f g d t b ti a d mo tal ty f 1946 50 d n g d t b t f l g n n a s oh rt

tive—a heavy increase in the numbers of deaths from cancer of the lung in future Copenhagen is to be expected as shown in the table

[This interesting analysis on the basis of cohorts indicates that the increase of mortality among men from cancer of the lung reflects a real increase in the frequency of the disease It also suggests a lag of at least 20 years between the beginning of exposure to a carcinogenic influence and death Though not specifically mentioned in this article the statistics of cigaret consumption in Denmark are consistent with the inference based on other statistical studies in Europe and America (see article by Doll p 132) of a causal relationship between smoking and lung cancer —Ed]

Superior Vena Cava Obstruction Syndrome in Bronchogenic Carcinoma Pathologic Physiology and Therapeutic Management B Roswit G Kaplan and H G Jacobson[9] (V A Hosp Bronx N Y) state that this syndrome in a patient with bronchogenic carcinoma is serious and will cause early death unless decompression therapy is promptly instituted The superior vena cava is the major vein for return of blood to the right heart from the head neck upper extremities and upper thorax It is vulnerable to obstruction because it is (1) thin walled with low venous pressure (2) locked in a tight compartment in the mediastinum (3) close to the right main bronchus and (4) encircled by lymph nodes that drain the right thoracic cavity and part of the left (Figs 16 19)

When the superior vena cava becomes obstructed collateral circulation takes over the burden of returning blood to the heart The patient s comfort and prognosis depend on the

(9) R d l gy 61 7 737 N mb 1953

ing statistical results Positive laboratory proof that cigaret smoking causes lung cancer is lacking but the evidence is highly suggestive

The historical statistical method has proved that patients with lung cancer have smoked cigarets more heavily than subjects without lung cancer but it gives no information about the degree of association between cigaret smoking and lung cancer This method entails many difficulties that may lead to erroneous conclusions Better statistical data are obtained by the follow up method of study collecting facts on habits or environments of large numbers of people who are followed for a number of years with a careful record also on all of their diseases Although time consuming and costly this method will provide accurate information The smoking habits of 204 000 men 50 69 were tabulated between January and June 1952 all will be carefully followed for a number of years to determine the epidemiologic relationship between cigaret smoking and lung cancer

Increase in Incidence of Carcinoma of Lung in Denmark 1931 50 J Clemmesen A Nielsen and E Jensen[8] (Danish Cancer Registry) report that the increase in mortality from cancer of the lung among men in Denmark during 1931 50 was due mainly to a real increase in the incidence of the disease although a slight accentuation of the increase during the years after 1940 which can be demonstrated for both sexes must be explained as due to improvements in diagnostic means

Analysis of the increase in mortality by Korteweg s method (calculated age incidence in a group—cohort—born in the same year rather than in a group living at one time) showed that the differences in crude mortality rates for cancer of the lung in Copenhagen provincial towns and rural areas may be ascribed to a delay in onset of the carcinogenic influence of about 8 years for provincial towns and about 10 years for rural areas Thus there is no reason to assume any carcinogenic influence of atmospheric pollution as far as Denmark is concerned

On the assumption that the carcinogenic influence does not begin earlier than age 15 or a few years later the authors believe that in Copenhagen it is about 20 years *from the begin*

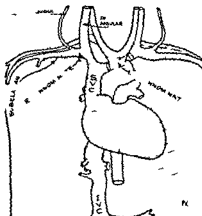
(8) Brit J Ca 7 1 9 Ma ch 1953

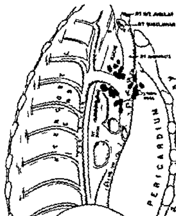
F g 20 (t p l ft) —I f ed ph tog ph of p fici l ous ll te al p t t w th pe na cava b tructo t po t bo e e try f ena zyg Not l borat p tt n of coll t ral on pp th

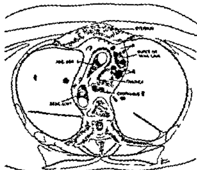
F g 21 (top ght) —I f d ph tog ph f p tient w th obstruction bel w entry f azyg n. El bo t pe fi l ll teral w e d m trated on lower bdomen d gr

F g 22 (bottom left) —Op cificat of ght subclavi a d ternal j gula e j n g right om nat w th pe cava blocked. St iki g d gr e of superfi l ll t al cul t t t l n t to yg n nd ght l

F g 23 (b tt m ght) —R ght om nat n d ts trib t p ified d dilat d. Ob tru t n t po t f entry t perior en N t d l t d p fi d yg S p r na ca ot fill d C der bl d p ll teral ci culat o may be n ted t ygos n n t se d ection t f ri v ca (Cou sy f Rosw t B *et al* R d logy 61 7 2 737 N mbe 1953)







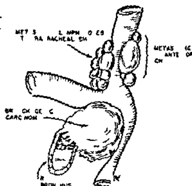


Fig 16 (top l ft) —Super or vena ca a and ts principal t buta es in r lation to the cic cag

Fig 17 (top right) —Illustrating v lne ble po t on of sup r v na a and vena a ygos n relat on to carc n ma f ght ma n br n hus and lymph node g oups us ally nvol d by b on hogen c a n ma *A* anter r prevascular nod *B* r ght pa atracheal n d s

F g 18 (bottom l ft) —C s ect n of supert med a ti l ompartm nt at l el of f r t ntercostal sp ce Note vul erabl pos t on f up or vena ca a n relat on to lymph nod groups u u lly nv lved by b onchial can *A* r ght a te r med t nal (prevascul r) lymph nodes *B* r ght parat ach al lymph node ha n

F g 19 (bott m right) —Dyn m hange in superior ven cava a d e azygos re ulti g f om bstruct on by bron hogen c ca c noma

(Courtesy of Rosw t B *et al* R d logy 61 722 737 Nov mbe 1953)

average 10 weeks Without treatment most of the patients would have died within a few weeks

The beneficial results of roentgen therapy were far more striking more objective in character and longer lasting than those obtained with nitrogen mustard Irradiation is without real hazard except in rare instances Radiation edema in the mediastinal area and radiation sickness were not encountered except in isolated cases and did not constitute an obstacle to completion of roentgen therapy

Intrathoracic Hibernoma Third Reported Case J Winthrop Peabody Jr Joseph Ziskind Howard A Buechner and Augustus E Anderson[1] (V A Hosp New Orleans) present one case

Man 31 had x ray evidence of a slowly enlarging density in



F 4—H gh pow ph t m cr g ph of h bernom h w ng h ct n ti l d m lt l l b w f t ll F of cu l w h m ll gg t t t t d lt f t ll (C t y of P body J W Jr t l New E gl d J Med 249 329 332 A g 0 1953)

(1) New E gla d J M d 249 3 9 33 A g 20 1953

efficiency of this collateral circulation (Figs 20 23) When the obstruction is above the azygos vein this major auxiliary vein takes over the function of the superior vena cava The veins of the neck shoulder girdles and upper thorax are prominent (Fig 20) Venous blood returns to the heart via the external jugular vein then to a superficial plexus on the anterior chest wall which connects with the perforating branches of the internal mammary and intercostal veins finally joining the azygos system to enter the superior vena cava below the obstruction (Fig 22)

When the obstruction is below the azygos arch or includes it the route of venous blood flow to the right heart is circuitous and complex and involves the support of the inferior vena cava The collecting circulation superficial and deep of the lower abdominal wall and groin is used for carrying blood to the inferior vena cava via the femoral and iliac veins (Figs 21 and 23)

Symptoms of superior vena cava obstruction include progressive dyspnea cough and orthopnea There is progressive edema of the head neck and upper extremities and a peculiar reddish cyanosis of the skin which grows more intense on recumbency Venous pressure in the upper extremities is elevated The site and nature of the obstruction as well as the pattern of the collaterals can best be determined by phlebography or angiocardiography

Of 38 patients with superior vena cava obstruction syndrome due to bronchogenic carcinoma 90% had anaplastic or undifferentiated lesions Thirty patients had right sided lesions All were seriously or critically ill when first seen Forty seven courses of therapy were administered to the 38 patients Of 28 courses of x ray therapy alone a satisfactory response was noted in 21 (75%) Of 15 courses of nitrogen mustard therapy alone a satisfactory response was noted in 12 (80%) A single combined course of irradiation and nitrogen mustard was given to four patients three had remissions

Remissions were characterized by relief from intractable respiratory distress pain and cough and abatement of cervicofacial edema and cyanosis often in 24-48 hours Objective evidence of improvement both clinical and radiologic was noted in more than two thirds of the patients who responded well subjectively The period of remission was 1 52 weeks

months has been reported in only one case Daniel S Lukas Charles T Dotter and Israel Steinberg[2] (Cornell Univ) report a case in which this association was suspected clinically and confirmed

Man 22 had had progressive exertional dyspnea since he was 2 and progressive cyanosis and clubbing of the toes (but not of the fingers) since he was 14 The left side of the chest had de



Fg 25 --Ang ocard g am tak n at tw econd n f ontal p je t n D l ted pulm y t fil d ce d g a rta th ough a l g h rt p tent d et rt r s s (Court sy f Lukas D S r l N w E gl d J Med 249 107 109 July 16 1953)

veloped less than the right Breath sounds were absent over the left hemithorax on percussion the right cardiac border was 1 cm left of th sternum various murmurs were heard He had polycythemia

Angiocardiograms (Figs 25 and 26) revealed the density in the left side of the chest seen on the conventional roentgenogram (Fig 27) to be composed entirely of cardiovascular structures The main stem pulmonary artery and all its ramifications to the right lung were greatly dilated Lung tissue in the upper left part

(2) New E gl d J M d 249 1 7 109 J ly 16 1953

the peripheral margin of the left upper lung field He had no respiratory symptoms or fever and tuberculin and histoplasmin skin reactions were both strongly positive Reaction to a coccidioidin skin test was negative No abnormalities were noted on bronchoscopy The mass already present in 1947 was three times as large in 1951 Although considered benign the mass was removed by thoracotomy It was located high within the thorax overlying the 2d rib and was removed after the parietal pleura was incised It was not fixed to the overlying pleura rib or intercostal muscles The postoperative course was uneventful and there was no recurrence during the 18 months of follow up

The gross lesion $3.5 \times 3 \times 1.4$ cm had spongy consistency and was finely lobulated Microscopically the tumor was divided into multiple lobules by delicate moderately vascular fibrous septa The lobules were composed of two distinct types of cells the predominant smaller cells (20 50 microns) being multilocular with central nuclei and the less numerous but larger cells (50 75 microns) looking like ordinary unilocular fat cells with typical signet ring nuclei (Fig 24) The multilocular cells varied in size tended to occur in closely packed masses separated by interspersed adult fat cells the cell membranes were well defined and the cytoplasm was eosinophilic and containing vacuoles The nuclei of the brown fat cells were round and basophil Oil red O stain for fat disclosed a largely lipid vacuolar content Intrathoracic hibernoma was diagnosed

[The authors concede that the existence in human beings of a structure homologous to the hibernating gland of animals is doubtful The name was given to this tumor however because of the similarity of the tissue and its brown color to hibernating gland fat Eighteen previously described cases of this remarkable tumor are cited from the literature in only two other instances arising within the chest—Ed]

CONGENITAL DISORDERS

Agenesis of Lung and Patent Ductus Arteriosus with Reversal of Flow Report of Case Agenesis of a lung is rare and usually is not recognized until after death In most of the 57 cases reported in the literature diagnosis was made at autopsy Increased frequency of antemortem recognition is probably due to wider use of bronchoscopy bronchography and angiocardiography in the investigation of obscure pulmonary conditions Pulmonary agenesis commonly is associated with congenital anomalies of other organs including the heart Its association with a patent ductus arteriosus which was recognized after death of the patient at the age of 4



Fig 27—P t te or w f b t. Hom g eou d ty fill l w h lf f th l ft d T b d pl d t l ft th he rt (Co rt y f Luk s D S *et al* N w E gl d J M d 49 107 109 J ly 16 1953)

complete absence of bronchial and pulmonary vascular elements unilaterally by bronchography and angiocardiography

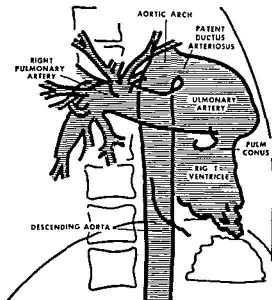
Bronchial Obstruction with Lobar Atelectasis and Emphysema in Cystic Fibrosis of Pancreas is discussed by Paul A di Sant Agnese[3] (Columbia Univ) based on 211 cases In all cases diagnosis was established by duodenal drainage or autopsy or both

Male infant had been in good health and nutrition until at 5 months he had a mild cough for a week and suddenly developed signs of consolidation of the right lung and acute respiratory distress Temperature rose rapidly to 40 C Chest roentgenograms one week later showed atelectasis of the entire right lung The

(3) P d t s 1 178 190 A g t 1953

of the chest was supplied by a branch of the right pulmonary artery and was herniated right lung The left pulmonary artery was absent in its place was a short patent ductus arteriosus 16 mm in diameter

The literature indicates that congenital aplasia is three times as common in the left lung as in the right It is more common in males than in females by a ratio of 3 2 Most



F g 26—D w g f F g e 5 (Co tesy of L k D S *et al* N w E gl d J Med 249 107 109 July 16 1953)

patients die in infancy or early childhood of respiratory infection or the associated congenital anomalies However in the 57 reported cases 3 patients lived to 58 65 and 72 Early diagnosis and prompt treatment of complicating respiratory infections may be expected to improve longevity

Agenesis should be suspected when physical and roentgen examinations reveal marked displacement of the heart and mediastinal structures to either side of the thorax without evident cause Diagnosis is established by demonstration of

deficiency of another liposoluble factor essential to normal functioning of the mechanisms for removal of bronchial secretions is possible

According to an alternate theory in cystic fibrosis there is a widespread disturbance of mucus secretion affecting many organs of the body (mucoviscidosis) However histologic changes in pancreas and in lungs are seldom similar Dilatation of bronchial glands due to apparent inspissation of secretions is rarely found in most instances the mucous glands of the trachea and bronchi appear normal or show hypersecretion

EFFECT OF LOBAR ATELECTASIS ON PROGNOSIS OF 194 PATIENTS WITH CYSTIC FIBROSIS OF PANCREAS*

	No. of Patients							
	Died at Age (yr.)			Total	Living at Age (yr.)			Total
	0-1	1-5	>5		0-1	1-5	>5	
With atelectasis (22 patients)	9	7	1	15 (68%)	2	3	2	8 (32%)
Without atelectasis (172 patients)	22	26	15	63 (37%)	6	54	51	111 (65%)

*Statistical comparison of total living and dead with and without atelectasis gives $X^2 = 5.98$ $P = 0.015$

microscopically similar to that in bronchitis Furthermore the material in the bronchial glands stains as mucus the material in the pancreas does not

Neither the hypothesis of a nutritional deficiency nor the concept of mucoviscidosis therefore explains completely the relation between pancreatic and pulmonary lesions The recent finding of an electrolyte abnormality of sweat secreting mechanisms in this condition supports the view that cystic fibrosis is a generalized disease of which the pancreatic and respiratory changes are only one expression Demonstration that a glandular system that does not produce mucus is affected casts doubt on mucoviscidosis as a body wide disturbance of mucous production

The cycle of events leading to pulmonary involvement is acute in patients with lobar atelectasis but is fundamentally the same except in degree for all patients with cystic fibrosis of the pancreas The following hypothesis is offered in expla

mediastinum and heart were shifted far to the right and the left lung was emphysematous (Fig 28) Fluoroscopic examination revealed obstructive emphysema with surprisingly little exchange of air during the respiratory cycle He died despite oxygen and penicillin therapy and tracheotomy and bronchoscopy The true diagnosis was not suspected clinically and only at autopsy were typical changes in the pancreas noted Besides atelectasis of the right lung general



F g 28 —Boy 5 month , w th coll ps d ght l g (Court y of d Sa t Agn se P A Ped t cs 12 178 190 Augu t 1953)

ized suppurative bronchitis and tracheitis and multiple lung abscesses were present

The relation of pulmonary involvement to pancreatic lesions is still a matter for speculation Vitamin A deficiency secondary to poor intestinal absorption leading to metaplasia of bronchial epithelium is no longer considered the main factor involved Normal serum vitamin A levels in 7 patients in the present series and metaplasia of bronchial epithelium in only 2 of 11 cases at autopsy are further evidence However

obstruction although concomitant variation in the distribution of blood probably occurs also Both arterial hypoxia and carbon dioxide retention tend to occur when there is inadequate ventilation of alveoli which continue to be perfused with the normal amount of capillary blood Carbon dioxide retention tends to occur also when large numbers of alveoli are inadequately perfused though normally ventilated because of the small volume of gas exchange in such alveoli Hypercapnia will not develop so long as an adequate ventilatory stimulus and the ventilatory capacity necessary to sustain sufficient compensatory hyperventilation of normally functioning alveoli are present and significant arterial desaturation will be delayed by the particular affinity of hemoglobin for oxygen even at low alveolar oxygen tensions

Although not clearly apparent from the studies chronic carbon dioxide retention and arterial unsaturation probably have unfavorable effects in these patients similar to those seen in chronic pulmonary emphysema due to other causes None of the patients had cor pulmonale but the pattern of pulmonary dysfunction may at times be conducive to its formation

In general the severity of impairment of pulmonary function closely parallels the chronicity and severity of the characteristic secondary bronchial and pulmonary infections A major goal of treatment is reduction of that element of bronchial obstruction contributed by respiratory infections

Kartagener s Syndrome in Children Lloyd B Dickey[5] (Stanford Univ) reports five cases one of which follows

Girl 6 weeks had dextrocardia but was asymptomatic Roentgenograms showed complete transposition of all the viscera with marked cardiac enlargement There was little change in her condition except for frequent cold until she was hospitalized at 4 months with acute pneumonia From this time on progress was slow She gained little weight and polycythemia developed Roentgenograms showed increased cardiac enlargement pronounced pulmonary vascular engorgement of the left lung field and atelectasis of the right lower lobe (Fig 29) At 10 months she had constant nasal discharge Bronchograms showed posterior di placement and partial obstruction to the right main bronchus atelectasis of the greater portion of the right lung with irregular small bronchial outlines and probably normal left bronchi She had many upper respiratory infections Cyanosis and dyspnea continued and marked

(5) D Ch t 23 657 666 J 1953

nation The cycle is usually initiated by acute respiratory infections causing increased mucus production Widespread and severe bronchial obstruction results and secondary infection of the obstructed air passages follows after a variable but usually short period The infected surface is thus suddenly and enormously increased In the preantibiotic era most patients died at this stage If the patient survives this cycle can be repeated again on the occasion of subsequent respiratory infections Any one of these episodes may be fatal

Lobar atelectasis is an expression of severe bronchial obstruction On the other hand lobar collapse favors the spread of infection to the involved pulmonary parenchyma and because of poor aeration of a large segment of lung contributes to severe anoxia A vicious circle is thus set up which contributes to the greater severity of symptoms and the malignant course of untreated cystic fibrosis with lobar atelectasis (table)

Pulmonary Function in Cystic Fibrosis of Pancreas John R West Sheldon M Levin and Paul A di Sant Agnese[4] (Columbia Univ) studied the pulmonary function in four boys and two girls aged 12 15 with cystic fibrosis of the pancreas associated with chronic pulmonary disease A characteristic pattern of dysfunction variable in severity was found Both ventilatory insufficiency (leading to dyspnea) and disturbances in gas exchange (leading to arterial hypoxia and carbon dioxide retention) may occur The former appears to be largely the result of factors which produce a diminished ventilatory capacity the most important probably being increased resistance to air flow within the tracheobronchial tree due to obstruction of the larger and smaller bronchi by accumulated secretions and purulent exudate The altered chest configuration secondary to emphysema may also be significant in some cases since thoracic hyperinflation places the muscles of respiration in a position of relatively poor mechanical advantage

Defective gas exchange seems to stem largely from disturbances in the normal relationships of alveolar ventilation to perfusion This seems in large measure due to uneven distribution of tidal air to the alveoli as a result of bronchial

(4) Pediatrics 13 155 164 February 1954

system (dextrocardia sometimes with other anomalies) (2) atelectasis (3) bronchiectasis and (4) sinusitis That the early development of bronchiectasis is influenced by a developmental error in the bronchi themselves is possible but direct proof is lacking Treatment consists of resection of affected pulmonary tissue as soon as the patient is a good surgical risk

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BRONCHIECTASIS AND CHRONIC BRONCHITIS

Bronchiectasis Study Centered on Bedford and Its Environs over five years (1947 51) is reported by N Wynn Williams[6] (Bedford Gen l Hosp) Bronchiectasis was confirmed by bronchograms in 166 patients a further 48 undoubted cases were discovered though not confirmed by bronchography because of the patient s age small respiratory reserve or refusal to consent to the procedure In addition there were 75 possible cases but diagnosis could not be established The proved ca es and the strongly suspected but not confirmed cases (214 in all) were therefore considered the approximate number discovered in a selected population of 150 000 during the five year period Exclusion of 14 patients because they died moved from the district or could not be traced left 200 persons with bronchiectasis living in the area at the end of 1951—an incidence of 1 3/1 000

The etiologic factors thought responsible for development of bronchiectasis were investigated and great care was taken to obtain an accurate history For a few patients without regular symptoms a history of a specific respiratory illness or an x ray typical of calcified primary tuberculosis was accepted as evidence of the antecedent factor Because of the difficulties of exact diagnosis the term pneumonia was used to include all acute respiratory infections Chronic or recurrent bronchitis and cough since infancy were considered factors rather than classed as of unknown etiology Congenital anomaly was not considered a cause as this is not susceptible to proof Pneumonia was judged to be responsible for 43% of the 166 proved cases pertussis and the infectious fevers for 16% recurrent bronchitis and cough since infancy for 21% pri

(6) B i M J 1 1194 1199 M y 30 1953

clubbing of the fingers developed She died at 14 months of acute respiratory infection

Autopsy revealed dextrocardia with situs transversus The heart was markedly distorted and complete transposition of the great vessels had occurred i e the aorta was on the left and pulmonary arteries on the right Interventricular septal defect was also present. Both lungs were reversed with two lobes on the right and four on the left The right lung was completely collapsed meaty red and firm the left large and fully expanded The right main bronchus



F g 29 —At lect s of ght l w lobe n g l 7 mo th (Courte y of D ckey L. B D Ch t 23 657 666 Jun 1953)

was completely collapsed and the cartilage in the posterior wall appeared to be absent

Four patients had complete situs inversus one dextrocardia only All of the children had pulmonary atelectasis one on the same side as the heart Four had bronchiectasis in the collapsed lobes on the left one (the youngest) beginning bronchiectasis or prebronchiectatic changes on the right All had clinical evidence of sinusitis Four of the five were girls The ages at which the disease was diagnosed were 6 weeks and 4 9 10 and 14 years The 10 and 14 year old patients were sister and brother All three children having lobar resections showed considerable improvement of pulmonary symptoms

Study of the literature and of these cases suggests that the sequence of events in the development of Kartagener s syndrome is (1) congenital anomaly of the cardiovascular

McKim (1953 54 YEAR BOOK pp 148 150) that pulmonary resection is not necessarily indicated in all resectable cases —Ed]

Chronic Bronchitis Factors in Pathogenesis and Their Clinical Application Neville C Oswald[7] states that the pathogenesis of chronic bronchitis is related to bronchial mucus and infection In health the mucus in the respiratory tract removes solid particles and noxious gases from the air In disease there are usually an excess amount of mucus and edema of the mucous membrane and the cilia are unable to remove the excess mucus thus interference with breathing occurs In health the trachea and bronchi are usually sterile but in disease they contain pneumococcus Hemophilus influenzae Staphylococcus aureus group A hemolytic streptococcus and Friedlander s bacillus There are components in mucus which promote lowered resistance to infection Infection external stimuli from atmospheric impurities and hereditary predisposition contribute to the onset of bronchitis Once the bronchi have become sensitized any irritant may aggravate symptoms the most prominent being excessive mucus This effect is *often overshadowed by the irritation caused by fog* damp ness and cold The hypersensitivity of chronic bronchitis is not allergic but is related to infection atmospheric pollution and climatic factors Asthma and bronchitis must be differentiated clinically

The first aim in treatment of chronic bronchitis is to prevent pathogenic organisms from reaching the bronchioles A clear warm dry atmosphere eradication of foci of infection in the nose and throat prevention of contact infection and prompt treatment of exacerbations reduce rate of progress of the disease Correct choice of antibiotics is difficult but a combination of penicillin and streptomycin is probably best for routine use

Air conditioning antibiotics and agents which reduce the viscosity of mucus may become effective in the treatment of chronic bronchitis Cortisone and corticotropin have not been found useful

[Th s and the related paper following by Reid reflect the emphasis which is placed n the Brit h viewpo nt on chronic bronchitis as a primary cause of pulmonary disabil ty and mortal tv This contrasts with the usual American attitude in which emphasis s placed primar ly on the associated parenchymal condition such as emphysema the bronchitis being regarded as secondary or at least not necessarily the cause That primarily bronchial

(7) La t 1 271 74 F b 6 1954

mary tuberculosis for 7% and mustard gas for 5% A number of miscellaneous causes made up the total

Analysis of the distribution and type of bronchiectasis revealed no great differences from those previously reported but the large number of cases due to primary tuberculosis and mustard gas was unusual The symptoms complained of were less severe and universal than those generally reported and approached those found in selected groups passed as fit for military service only five patients under 60 were unable to work Only three patients had normal posteroanterior x rays Patients whose diagnosis had been made in teaching or large hospitals had more extensive disease and also severer symptoms than the others Patients with disease of less than lobar extent had fewer symptoms

The period of observation averaged three years during which there were six deaths all in patients with bilateral involvement or due to complications not related to bronchiectasis There were no deaths from pneumonia or other pyogenic complications The condition of the other patients changed little Treatment was mainly medical but six patients underwent resection

Bronchiectasis is usually regarded as a serious disease commonly causing much disability requiring surgery if at all possible and leading to early death The present survey suggests that the prognosis in medically treated patients is not so bad The one time common causes of death pneumonia and other pyogenic complications have ceased to be important and a far higher proportion of patients in the future will die of unrelated diseases and of cor pulmonale secondary to extensive bronchiectasis None of the six who died could at any period of illness have been considered for operation either because of the large areas involved or because of other factors It may not be justifiable to advocate surgery whenever this is possible Many patients are likely to remain well and be little inconvenienced by their disease if competently treated by postural drainage and antibiotics This applies particularly to the operable group

[This superb study should help to correct prevalent misconceptions concerning the natural history of bronchiectasis It is also the first, to my knowledge to give any reliable estimate of the incidence of the disorder in the general population The observations support the contention of

disease and include pneumonia organization of pneumonic exudate edema emphysema patches of collapse and mucus and pus in alveolar spaces These changes cause serious disturbance of the normal lung pattern Though the individual lesions may be small their effect is cumulative and because of their location they cause severe functional disability

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EMPHYSEMA

Surgical Treatment of Bullous Emphysema Contributions of Angiocardiography According to Laurence Miscall and Robert W Duffy[9] (New York City) *bullous emphysema may* assume several forms characterized by (1) discrete giant bulla (2) conversion of an entire lobe into a flimsy voluminous structure as a result of even progression of the diffuse basic emphysematous change and (3) recurrent persistent or tension pneumothorax In this last group the importance of rupture of small blebs has been clearly demonstrated

In bullous emphysema bronchial obstruction even of intermittent type may have serious consequences Excessive local overdistention caused by persistent check valve type of obstruction in a segment or lobe often has precipitated grave pulmonary symptoms These have appeared when respiratory function already reduced by actual replacement of pulmonary parenchyma by the bullous disease has been reduced to critical levels by concomitant compression of the remaining lung The similarity of symptoms and signs resulting from the complex pathologic changes usually makes recognition of the lesions by clinical examination alone impossible Distressing dyspnea is a constant complaint Its cyclic exacerbation with upper respiratory infections is due to increased obstructive local emphysema constantly aggravated by coughing and excessive tenacious secretions

Although physical examination is satisfactory as an aid in evaluating the need for emergency therapy it fails to provide the information necessary for correct application of elective pulmonary resection Meticulous serial roentgenographic check of the clinical observations is essential Tomography provides important data such as size position and pattern of

(9) D Ch t 24 489-499 N mbe 1953

disorders with abnormal secretions may cause extreme pulmonary insufficiency is perhaps most clearly established in the instance of the pulmonary changes associated with cystic fibrosis of the pancreas (see article by di Sant Agnese p 145 and by West *et al* 148) To what extent the different varieties of pulmonary emphysema and fibrosis commonly seen in adults may result from chronic bronchial infection and to what extent from other more obscure factors is difficult to estimate This approach by defining the morbid anatomy bacteriology and other pathogenetic factors in chronic bronchitis may lead to a better understanding and to more effective preventive applications of therapeutic measures The great importance in functional terms of controlling acute bronchopulmonary infection in patients with established pulmonary insufficiency was well demonstrated by Stone and co workers (1953 54 YEAR BOOK pp 137 139) —Ed]

Pathology of Chronic Bronchitis was studied by Lynne McA Reid[8] (London) in specimens obtained at autopsy bronchoscopic biopsy and operation Peripheral parts of the lung were examined by serial sections of the primary and secondary lobules Lesions of different age and severity may be found in different areas of the same lung The principal feature of early cases is hypertrophy of the mucus secreting elements of the bronchi causing excess mucus in the air passages In sections stained by the periodic acid Schiff method there is an increase in number of goblet cells even in the bronchioles where normally they are scarce The mucous glands which are confined to the bronchi also show hypertrophy and their ducts are often dilated On bronchography they give the appearance of diverticulosis There is usually edema of the bronchial wall with swelling of the basement membrane and some infiltration by small round cells Excess mucus in air passages impairs respiration and provides a mechanism for spread of infection along the airways toward the vital peripheral lung units

In advanced cases further significant lesions are found in the terminal parts of the air passages The bronchi show the same changes seen in the early stages though there may be acute inflammation associated with terminal infection The bronchioles show hypertrophy of goblet cells and purulent bronchiolitis Abscess cavities may form in the small bronchioles and the bronchioles are cut off from their peripheral branches and alveoli with resulting derangement of function The small bronchioles may become obliterated or dilated Alveolar changes in advanced cases are due to bronchiolar

(8) Lan et 1 275 278 F b 6 1954

expansion of the remaining compressed lung tissue Post operative results in a large series of cases have demonstrated that such a course can be anticipated regularly by careful evaluation of function in a relatively quiescent period Complete absence of symptoms may be fortuitous and does not constitute an absolute contraindication to surgery since such security may be temporary in view of the ever present danger of rupture or infection The most reliable indication for surgery has been evidence sometimes only intermittently present of significantly diminished pulmonary function and a lesion which conforms to the previous criteria Although the emphysematous changes in the remaining lung may conceivably progress duration of significant relief (up to five years in some cases) has indicated that surgery is a valuable method of rehabilitation

Treatment of Hypertrophic Emphysema by Pneumoperitoneum Bertram Mann and Edmond A Murphy[1] at weekly intervals for three months introduced 300 550 ml air under the diaphragms of nine men and one woman aged 38 69 with advanced hypertrophic emphysema and recorded the vital capacity and maximal breathing capacity at monthly intervals Control studies consisted of measuring vital capacity and maximal breathing capacity of the same patients before the experiment began following mock pneumoperitoneum (without telling the patient) and after the experiment Only one patient was consistently improved symptomatically and in maximal breathing capacity during presence of pneumoperitoneum Otherwise there was no consistent change in either vital capacity or maximal breathing capacity Clinical improvement could not be correlated with any change in respiratory function

Results were disappointing and do not warrant the amount of labor and time involved in giving weekly refills The favorable results reported by other investigators were probably due to extraneous influences of pulmonary function and to increased efficiency and mental co ordination in performance of the tests

Treatment of Pulmonary Emphysema with Aerosolized Bronchodilator Drugs and Intermittent Positive Pressure Breathing Ward S Fowler H Frederic Helmholz Jr and

(1) Th 9 87 90 M h 1954

the lobes fissures bronchi and vessels Angiocardiography is reliable in demonstrating the extent of irreversible changes In moderately advanced emphysema the vessels are reduced in size and number and in far advanced cases they may be absent The vessels in compressed lung are crowded together and fill poorly That this reduction in number and size of the peripheral vessel branches is temporary when due to compression has been substantiated by many postoperative ob



Fg 30 (l ft) —P p t gi ca d ogram of m n 56 t tally disabl d by b l t l bull s emphy m Pulm n y l t n ab t pp l b at s tes of g t bull nd b l p lm n y l t m k dly p d
Fg 31 (ght) —A g o d g m n m th ft l ft pper l b t my R e p n f left l we l b all w d et f p lm y culat n Not th t p ce f l ft b la cy t d g n t us t f en e w th p lm n ry cul t on. T nt at l ft p x p e t fu th o d tent n of l g C ul t n f r ght l g ha ged P t t wa bl to t n t w k d was st ll w k g th e y a s ft pe at on If ec y ght uppe lob ctomy can b d
(Co rt y f M all L nd D ffy R W D Ch t 24 489 499 N v mber 1953)

servations After resection of an emphysematous portion and expansion of the residual lung prompt reversal toward the normal vascular pattern with improved filling and distribution of the vessels has occurred (Figs 30 and 31) Because of its greater safety and reliability angiocardiography is preferable to bronchography

Indications for emergency surgery have been well documented but the role of elective procedures has been neglected Elective measures should be used when the volume of destroyed lung is sufficiently localized to permit clean excision and when improved pulmonary function can be expected from

expansion of the remaining compressed lung tissue Post operative results in a large series of cases have demonstrated that such a course can be anticipated regularly by careful evaluation of function in a relatively quiescent period Complete absence of symptoms may be fortuitous and does not constitute an absolute contraindication to surgery since such security may be temporary in view of the ever present danger of rupture or infection The most reliable indication for surgery has been evidence *sometimes only intermittently* present of significantly diminished pulmonary function and a lesion which conforms to the previous criteria Although the emphysematous changes in the remaining lung may conceivably progress duration of significant relief (up to five years in some cases) has indicated that surgery is a valuable method of rehabilitation

Treatment of Hypertrophic Emphysema by Pneumoperitoneum Bertram Mann and Edmond A Murphy[1] at weekly intervals for three months introduced 300 550 ml air under the diaphragms of nine men and one woman aged 35-69 with advanced hypertrophic emphysema and recorded the vital capacity and maximal breathing capacity at monthly intervals Control studies consisted of measuring vital capacity and maximal breathing capacity of the same patients before the experiment began following mock pneumoperitoneum (without telling the patient) and after the experiment Only one patient was consistently improved symptomatically and in maximal breathing capacity during presence of pneumoperitoneum Otherwise there was no consistent change in either vital capacity or maximal breathing capacity Clinical improvement could not be correlated with any change in respiratory function

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(1) Th 9 87 90 M b 1954

R Drew Miller (Mayo Clinic) studied 41 patients with chronic diffuse obstructive emphysema to evaluate the results of two to three weeks of treatment with inspiratory positive pressure breathing of oxygen inhalation of an oxygen generated aerosol of isopropyl arterenol (isuprel®) and both combined Oxygen was administered to 22 patients by intermittent positive pressure breathing (IPPB) four times daily for 20 minutes each time for an average of 12 consecutive days Oxygen and aerosol of isopropyl arterenol solution (isuprel®) in 0 5 ml doses of 1 200 solution with 0 5 ml distilled water aerosolized by DeVilbiss no 40 nebulizer were administered by IPPB four times daily for 20 minutes each for an average 10 6 days to 10 patients who had earlier had 10 7 days of oxygen IPPB treatment and for an average of 13 2 days to 10 patients who had received no previous treatment 10 other patients were treated initially for an average of 7 days with oxygen isuprel® aerosol and then for an average of 7 days more with oxygen isuprel® IPPB

The results judged chiefly by symptomatic improvement and by various pulmonary function tests indicate that aerosolized isuprel® excelled oxygen IPPB alone and equaled the combined treatment including isuprel® aerosol and IPPB Moderate symptomatic improvement was obtained by most patients when an oxygen generated isuprel® aerosol was administered either with or without IPPB The persistence of dyspnea although variably reduced and the unchanged results of pulmonary function tests indicate that the basic bronchopulmonary changes were not altered by any of the treatments

Most of the patients had pronounced emphysema but were ambulatory and resting arterial oxygen saturation in them was normal Only the results of short term therapy were evaluated since these patients were in less need of mechanical assistance in inspiring room air oxygen or aerosol than more seriously ill patients with severe hypoxemia and CO retention For the latter IPPB machines are among the several available devices that can provide pulmonary ventilation

[These results indicate that in chronic emphysema there is little advantage in administration of bronchodilator aerosols by IPPB rather than by simpler means In the following report the clinical results in contrast

( ) P oc St ff M et M y Cl n 28 743 751 D 30 1953

are considered better with IPPB and aerosols than with aerosols alone and there are objective measurements which tend to support this clinical impression Nevertheless it appears from the evidence in these two papers that the principal usefulness of this type of apparatus is not in the routine management of ambulatory patients with chronic emphysema but in the treatment of pulmonary emergencies such as severe asthma pulmonary edema respiratory acidosis and respiratory depression due to drugs —Ed.]

Intermittent Positive Pressure Breathing Its Use in Inspiratory Phase of Respiration M S Segal A Salomon M J Dulfano and J A Herschfus[3] (Tufts College) using the Bennett apparatus applied intermittent positive pressure during inspiration to 203 patients with bronchial asthma (95) chronic pulmonary emphysema (74) bronchiectasis (20) pulmonary edema (4) bronchial and bronchiolar irritation secondary to irritating gases and fumes (3) respiratory depression due to barbiturates morphine or carbon dioxide (5) or chest trauma (3) Either air or oxygen was used with or without a bronchodilator solution in a nebulizer attached to the apparatus Neo suprel® isuprel® or vaponefrin was used as a bronchodilating solution and some patients also received pancreatic dornase by aerosol Treatments were given one to three times daily for about 20 minutes at a time and the course of treatment lasted 5 60 days

Clinical results in most patients were good or excellent and in many cases lifesaving Treatment was most helpful in bronchial asthma with bronchospasm and bronchial obstruction the chief factors contributing to discomfort The clinical results in chronic pulmonary emphysema were good but not as good as in bronchial asthma Combining intermittent positive pressure breathing during inspiration with bronchodilating aerosols excelled either alone

Vital capacity timed vital capacity and maximal breathing capacity immediately after intermittent positive pressure breathing with the Bennett apparatus alone were usually lower than before the treatment despite good clinical results Combining intermittent positive pressure breathing by the Bennett apparatus with bronchodilating aerosols improved these indexes of respiratory function The decrease in respiratory function as measured by vital and breathing capacities after pressure breathing may be due to pulmonary congestion or temporary fatigue

(3) N w E gl d J M d 250 5 32 F b 11 1954

Pulmonary Hypertension III Physiologic Studies in Three Cases of Carbon Dioxide Narcosis Treated by Artificial Respiration Frank W Lovejoy Jr Paul N G Yu Robert E Nye Jr Howard A Joos and John H Simpson with S John Vernarelli and Carol Gouverneur[4] (Univ of Rochester) discuss three patients with severe pulmonary insufficiency who became comatose after the administration of oxygen The coma was associated with severe hypercapnia and respiratory acidosis In advanced pulmonary emphysema and fibrosis the ventilatory function of the lungs is impaired and carbon dioxide tension of arterial blood rises The respiratory

TABLE 1 — ARTERIAL BLOOD GAS STUDIES IN ONE PATIENT BEFORE AND DURING OXYGEN THERAPY

Breathing	Pco (mm. Hg)	Po (mm. Hg)	CO Content (vol %)	O Content (vol %)	O S (%)	pH	
						Calculated	Observed
Room air	9	24	36 9	8 55	33 7	7 36	
Oxygen by mask 2 L./minute for 30 minutes	97	54	36 7	18 66	3 5	7 25	7

center adjusts to high tensions of CO Breathing is stimulated in part by the effects of anoxia on the chemoreceptors in the aortic and carotid bodies With oxygen therapy the hypoxic stimulus is eliminated leading to further hypoventilation and greater CO retention initiating a vicious cycle and resulting in coma Carbon dioxide retention is the primary problem and ventilation has to be increased to restore homeostasis Since such patients have lost the normal centrogenic and chemoreflexic drives for breathing some mechanical aid to ventilation is needed In two cases mechanical ventilation in the Drinker respirator resulted in recovery

The course of each comatose patient was followed by means of serial arterial blood gas analyses and pH estimates Each patient had polycythemia Lung volume studies after treatment demonstrated that pulmonary insufficiency was due chiefly to pulmonary fibrosis in two cases and to severe emphysema in the third Cardiac catheterization after therapy disclosed moderate pulmonary hypertension normal cardiac output and moderately increased total pulmonary resistance in each case One patient had markedly elevated pulmonary

(4) Am J Med 16 4 11 Ja y 1954

artery pressure before therapy The clinical response to mechanical ventilation slow in each case required an average of 9 10 days in the respirator before chemical improvement stabilized Even after compensation of respiratory acidosis it took several days for the respiratory center to adjust to relatively normal CO_2 tension

Mechanical ventilation requires constant nursing and

TABLF 2—CARDIAC CATHETERIZATION STUDIE IN ONE PATIENT

	(F eathing O_2) P e tr atment		(Breathing Air) Post-treatment	
	Brach al A t ry	Pulmo- n ry Artery	B a t l Artery	Pulmo- nary Artery
Blood Gas An lysis				
CO_2 cont nt (l %)	85 1	87 9	51 4	53 8
O o tent (vol)	12 8	8 7	15 6	11 9
O_2 capac ty (ol)	5 31		18 0	
O_2 saturation (%)	80 5	34 5	86	66
pH	7 5	7 19	7 4	7 37
P_{co} (mm. Hg)	77		45	
P_{o_2} (mm Hg)	39	1	59	41
Pressures (mm Hg)				
Systol /Diastol		(7/ 6	13 /80–	38/10–
		91/50	147/88	51/20
Me		60 0	100	28 9
Ca diac Output				
O consump on (cc /M²/m)			136	
A V O diff nc (vol %)	4 0		3 65	
Ca diac nd (L /M /m n)			3 72	
Resist c (dynes-sec -cm)				
Total pulmo ry			394	
Pulmon ry a teriol			22	

medical supervision Serial arterial blood gas analyses and pH estimates will disclose by continued high CO_2 tension of arterial blood either inadequacy of the airway or of mechanical ventilation Mechanical ventilation not only blows off CO but also enables oxygen therapy to relieve severe hypoxemia Antibiotics and digitali by relieving intercurrent infection and trengthening cardiac muscle probably contribute to the success of therapy

Woman 42 with hi tory of bronchial asthma repeated re pira

Pulmonary Hypertension III Physiologic Studies in Three Cases of Carbon Dioxide Narcosis Treated by Artificial Respiration Frank W Lovejoy Jr Paul N G Yu Robert E Nye Jr Howard A Joos and John H Simpson with S John Vernarelli and Carol Gouverneur[4] (Univ of Rochester) discuss three patients with severe pulmonary insufficiency who became comatose after the administration of oxygen The coma was associated with severe hypercapnia and respiratory acidosis In advanced pulmonary emphysema and fibrosis the ventilatory function of the lungs is impaired and carbon dioxide tension of arterial blood rises The respiratory

TABLE I — ARTERIAL BLOOD GAS STUDIES IN ONE PATIENT BEFORE AND DURING OXYGEN THERAPY

Br h g	P_{aco} (mm Hg)	P_{ao} (mm. Hg)	CO Con en (vol %)	O Con (vol %)	O S (%)	pH	
						Cal l ed	Observed
Room	79	24	36 9	8 55	33	7 36	
Oxyge by mask 2 L. m for 30 mın rs	9	5	36	18 66	73 5	7 25	6

center adjusts to high tensions of CO_2 Breathing is stimulated in part by the effects of anoxia on the chemoreceptors in the aortic and carotid bodies With oxygen therapy the hypoxic stimulus is eliminated leading to further hypoventilation and greater CO retention initiating a vicious cycle and resulting in coma Carbon dioxide retention is the primary problem and ventilation has to be increased to restore homeostasis Since such patients have lost the normal centrogenic and chemoreflexic drives for breathing some mechanical aid to ventilation is needed In two cases mechanical ventilation in the Drinker respirator resulted in recovery

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(4) Am J Med 16 4 11 J y 1954

with oxygen therapy but the PA_{CO_2} increased further and respiratory acidosis ensued

The next day cardiac catheterization (Table 2) revealed severe pulmonary hypertension of the precapillary type Because of failure to improve she was placed in a body respirator on the fourth hospital day The course was followed by arterial blood gas studies (Fig 32) At first because of difficulty in synchronizing with the respirator her chemical status deteriorated but with training and by increase of the rate and the inspiratory and expiratory pressures of the respirator both CO_2 retention and respiratory acidosis gradually improved Mechanical respiration was discontinued intermittently one week later and stopped entirely in a few more days Lung volume studies before hospital discharge disclosed the presence of predominant pulmonary fibrosis

Cardiac catheterization 2½ months later disclosed striking improvement over almost all pretreatment values Mean pulmonary arterial pressure had fallen from 60 to 29 mm Hg and oxygen saturation of the arterial blood had risen The PA_{CO} and oxygen capacity of the blood (hemoglobin) had declined to normal Respiratory acidosis had been corrected Total pulmonary resistance was elevated and pulmonary arteriolar resistance also was somewhat above normal

[The now well konwn adverse effects of continuous oxygen therapy in respiratory acidosis are here illustrated in complete detail as well as the corrective effects of artificial respiration The cumbersomeness and the difficulties of synchronization in mechanical respiration make this a formidable method of treatment It will be interesting to see whether by omission of oxygen correction of the secondary polycythemia by phlebotomies control of infection by antimicrobials and the use of diamox® (see following article) the necessity for artificial respiration may not be limited to the exceptional case —Ed]

Effects of Carbonic Anhydrase Inhibitor "6063" on Electrolytes and Acid Base Balance in Two Normal Subjects and Two Patients with Respiratory *Acidosis* *were studied by* Judith Nadell[5] (Columbia Univ) The two patients had pulmonary emphysema and respiratory acidosis The electrolyte changes in both groups were essentially the same Administration of 6063 caused a transient increase in urinary pH increase in urinary CO sodium potassium and phosphate and a fall in urinary ammonia This was associated with a fall in arterial pH and CO_2 content and a transient decrease in the plasma potassium concentration After two to three days the daily urinary excretion of electrolytes returned to the levels of the control period but the plasma CO_2 content remained depressed during the entire period of drug adminis

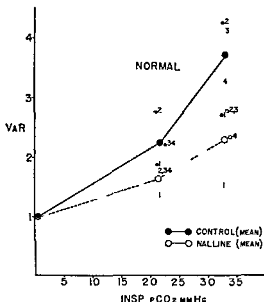
(5) J Cl I t 32 62 629 J ly 1953

tory infections and progressive dyspnea on exertion had chronic cough and ankle edema that failed to respond to digitalis therapy and salt restriction Dyspnea and cyanosis were moderate at rest neck veins were moderately distended and dulness and rales were noted in both lung bases Numerous wheezes and rhonchi were present throughout both lungs The heart was slightly enlarged to

Fig 3 —Se al blood at d d r ng d two months aft ho p t l t pH val es were all det m ed d re tly (C tesy f Lo jo F W J r f Am. J Med 16 4 11 Ja u ry 1954)

the left and heart rate was 138/minute Blood chloride content was 90 mEq and CO combining power 42 mM /L Venous pressure was 270 mm water and arm to tongue and arm to lung circulation times were 20 and 14 seconds Hemoglobin content was 19 Gm /100 ml Several hours after digitalis therapy and 7 L oxygen/minute she became comatose Arterial blood samples were drawn later that day during breathing of room air and again after about 30 minutes of breathing 2 L CO_2/minute by mask (Table 1) Oxygen saturation of arterial blood rose appreciably

2 mg nalline® in four normal persons Nalline® a potent re spiratory depressant lowered the sensitivity of the respiratory center to carbon dioxide by approximately 50% (Fig 33) Nalline® was given to three patients with pulmonary emphy sema and respiratory acidosis in 10 mg doses intravenously and its effect on respiration compared with pretreatment con trol measurements (Fig 34) Nalline® caused more insensitiv



Fg 33—Ventl t on po se t ca bon d d n ormal bj ct. O di t l l tlt t (l R) b sc sa p d bo d i p l d d l l ft n ll ® (Cou t y of T y S M d M thoef J C New E gl d J M d 249 886-890 N 26 1953)

ity to carbon dioxide than was present in the control period The patients felt drowsy and generally indifferent In dogs with acute respiratory depression from carbon dioxide nar cosis the drug had no effect on respiratory ventilation

The study proves that nalline® even in small doses is a respiratory depressant and does not support the suggestion that it might be beneficial in respiratory acidosis not related to drug intoxication nor the contention that its primary

tration and the arterial pH only gradually rose to control levels

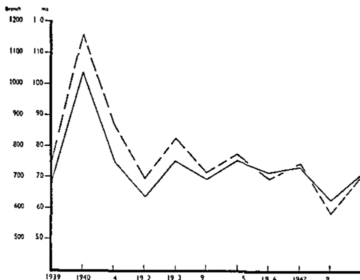
The two control subjects were asymptomatic during the entire period of study One patient who had previously been comatose because of respiratory acidosis and who had required the daily use of a respirator was maintained in an alert state outside the respirator for two separate periods while receiving 6063 With continued use of the drug he remained alert without use of the respirator for three months No late side effects were observed In the other patient with respiratory acidosis but without antecedent alteration of consciousness marked drowsiness developed 14 days afer initiation of therapy This was not correlated with changes in arterial pH or CO_2 These symptoms disappeared promptly when the dose was decreased from 10 to 5 mg/kg/day No other toxic manifestations or clinical changes were noted

Rebound phenomena after cessation of 6063 administration were prominent There were a decrease in urinary excretion of sodium an increase in urinary ammonia and a rise of blood pH to above control values for three to seven days

[The use of diamox® in respiratory acidosis is promising and the effects are sometimes dramatic The sustained depression of the plasma CO content despite the rapid return of urinary electrolyte excretion to pre treatment levels results in the maintenance of the favorable clinical effects during prolonged periods of administration These favorable effects relate not alone to clearing of comatose states but to relief of dyspnea and objective improvements in pulmonary function Much is unexplained concerning the mechanisms but the primary action is believed to be inhibition of carbonic anhydrase activity in the kidney This can explain the immediate effects on acid base equilibrium by limiting the availability of hydrogen ion and so resulting in the increased urinary excretion of bicarbonate and the decreased urinary excretion of ammonia Sodium potassium and phosphate excretion are increased secondarily to these reactions The later urinary compensation despite continued drug administration and return of electrolyte excretion to pre treatment levels without accompanying rise in plasma CO_2 content is less readily explained Time factors in spacing of doses may be important not only in maintaining the favorable therapeutic effect on respiratory acidosis but in maintaining a physiologic equilibrium of blood electrolytes Further studies of this interesting development will be eagerly awaited —Ed]

Respiratory Depressant Action of n Allylnormorphine in Normal Subject and in Patients with Respiratory Acidosis Secondary to Pulmonary Emphysema S M Tenney and J C Mithoefer with S L Hutchins[6] (Univ of Rochester) studied the respiration before and after intravenous administration of

(6) New Engl nd J Med. 249 886-890 Nov 26 1953

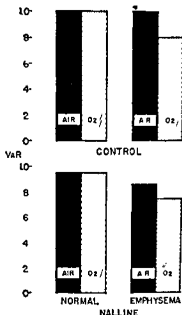


F g 35—D th f thm d f m b h t 1939 40 C t l = J thm b k l e = b h t (C t y f W ll m D A Th 8 137 140 1953)

by the author Analyses indicated that asthma carries a definite mortality rate from status asthmaticus in Great Britain and that the asthmatic patient especially at risk is the one liable to recurrent status asthmaticus Deaths from status asthmaticus occur predominantly in asthmatics over 30 and in those with chronic asthma Infection probably plays a dominant part in the cause of such deaths

Clinical and Pathologic Study of Fatal Cases of Status Asthmaticus is reported by J C Houston S De Navasquez and J R Trounce[8] (Guy s Hosp London) Of nine patients none had evidence of respiratory infection or pulmonary heart disease The lumens of all bronchi and bronchioles examined microscopically were almost entirely filled with mucus The mucus stained homogeneously bright red with periodic acid Schiff stain and contained richly cellular spirals composed of eosinophil polymorphonuclear leukocytes and detached cili

(8) Th 8 07 213 S pt mb 1953



F g 34 —Cha ge n al eol r t lat on rat os (m n v l es) on b ath ng of 100% o yg b f e d aft ll ® (Co t y f T ey S M a d M thoef r J C New Engla d J Med 249 886-890 Nov 26 1953)

mechanism of action is one of stimulating the central nervous system especially the respiratory center

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BRONCHIAL ASTHMA

Deaths from Asthma in England and Wales D A Williams[7] (Cardiff) studied the Registrar General s reports for England and Wales and found that in 1938-49 35 173 deaths were attributed to asthma an average of 2 931 each year For these years asthma accounted for 0 6% of all deaths in England and Wales (Fig 35) Asthma deaths expressed as death rates per 100 000 of the living population averaged 7 07 These figures are considerably higher than the corresponding figures in the United States

Death from status asthmaticus was confirmed at autopsy in 140 cases from the literature and in 21 of 41 cases examined

(7) Tho ax 8 137 140 J e 1953

attack the greater will be the loss of ciliated epithelium A stage may be reached at which mucus can no longer be removed from the smaller bronchi clinically this stage is characterized by lack of response to antispasmodics In status asthmaticus this is fatal Most patients with a clinical diagnosis of status asthmaticus recover presumably there is only partial bronchial plugging with bronchial spasm which in time responds to treatment

In all nine patients asthma had developed in adult life in five the age of onset was 40 or over This suggested the possibility that asthma developing late in life is particularly likely to cause death from status asthmaticus

Aerosol Trypsin Therapy in Treatment of Asthma Homer E Prince Richard L Etter and Richard H Jackson[9] (Houston) report results of therapy in nine patients with atopic bronchial asthma and secondary infection including one with emphysema and eight patients with chronic asthmatic bronchitis (primarily infectious asthma) including two with emphysema All received by aerosol 0 25 cc of 1 1 000 aqueous epinephrine before starting treatment with tryptar® (crystalline trypsin) The tryptar® freshly dissolved in Sorensen s buffered phosphate solution was administered by Pen i sol aerosol apparatus using oxygen for nebulization Two patients received only one treatment and 15 received one or more additional treatments daily the greatest number being 10 for a patient who received 1 250 000 units

The 17 patients received a total of 72 aerosol treatments with tryptar® in doses varying from 62 500 to 250 000 units Only two obtained clearcut beneficial results and five were questionably benefited In one patient asthma was increased on two occasions and another complained of laryngeal irritation after each treatment

Use of tryptar® aerosol to increase expectoration in asthmatic patients with either primary or secondary bronchitis proved disappointing Bacterial infection is frequently allergenic in allergic patients and tryptar® only temporarily cleanses the bronchial tree and does not eradicate the infecting agent thus the mucopurulent exudate continues to be produced

[Farber and his associates (p 211) have reported sensitivity reac

(9) A All gy 12 25 29 J n F b 1954

ated epithelial cells intimately mixed in varying proportions (Fig 36) It appeared to be a continuous mass extending from the major bronchi down to the bronchioles and only partially separated at various points from the bronchial wall The wall showed these characteristic changes (1) partial or complete detachment of superficial ciliated epithelium from all bronchi leaving only a thin layer of nonciliated cells as a lining which was continuous with the normal and similar lining of the bronchioles (2) bronchial constriction (3)

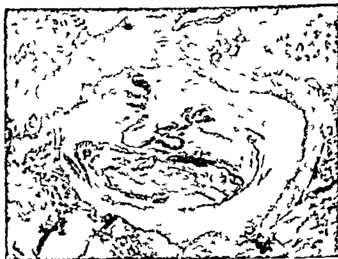
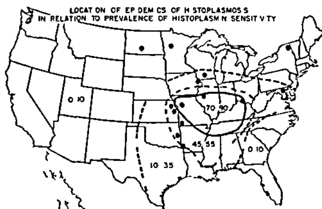


Fig 36—M cu pl g w th e t l p ral f d t ched p th l m sm ll b onch H m to yl -eos n e l ced fr m × 40 (C rt y of Hou t n J C. et l Tho 8 207 213 S pt b 1953)

thickening of the so called basement membrane of the wall and (4) widespread emphysema

Plugging of the smaller subdivisions of the bronchial tree with mucus is common in patients with status asthmaticus and the consequent interference with pulmonary ventilation is a major cause of death It has not been generally appreciated that widespread detachment of ciliated epithelium is an equally constant and characteristic finding Presumably in a short attack of asthma the amount of ciliated epithelium lost is insufficient to prevent the expulsion of mucus and after the attack the bronchial epithelium regenerates The longer the

ized malaise followed in 12 36 hours by chills fever and prostration Chest complaints were characteristically mild with vague discomfort and nonproductive cough Pronounced weakness was uniformly present and occasionally dyspnea occurred Fever and acute illness lasted from a few days to two or three weeks The weakness lasted much longer fre quently for many months A productive cough was often noted after the first week but in general the physical findings



F g 37 (Co rtesy f F l w M L d G y t n J T Am R T be c. 68 307 320 September 1953)

and symptoms in the chest were remarkably few in relation to the extensive involvement seen on x ray

The chest x ray during the first week might be normal but extensive bilateral involvement developed rapidly The typical picture consisted of numerous and widely disseminated dis crete infiltrations which varied in size from small fine granu lar lesions through a snowflake appearance to discrete nodules In mild cases there were fewer lesions sometimes localized Hilar lymph node enlargement was usually present The roent gen abnormalities tended to clear in two to six months al though some lesions persisted apparently in the form of generalized fibrosis Whether apparent clearing occurred or not a high percentage of patients eventually had pulmonary calcification

tions including asthmatic attacks apparently induced by trypsin inhalations or trypsin combined with desoxyribonuclease in pulmonary tuberculosis patients They also noted increased metaplasia in the cellular components of sputum —Ed]

Evaluation of Oral Bronchodilator Agents in Patients with Bronchial Asthma and Pulmonary Emphysema was carried out by Hylan A Bickerman Gustav J Beck Sylvia Itkin and Fred Drimmer[1] (Columbia Univ) Compound 1313 (3 4-dihydroxyisopropylamino propiophenone hydrobromide) was clinically ineffective in most of the 82 patients studied No significant changes in vital capacity or maximal breathing capacity were noted with this drug or with a placebo Moderate to excellent clinical relief of bronchospasm occurred in 52% of 94 patients taking nephenalin® (n isopropylarterenol hydrochloride theophylline ephedrine sulfate and phenobarbital) 72% of 155 taking dainite® (ephedrine hydrochloride aminophylline aluminum hydroxide ethyl aminobenzoate and sodium pentobarbital) and 75% of 64 taking cardalin (aminophylline aluminum hydroxide and ethyl aminobenzoate) Ventilatory function studies showed a mean rise of approximately 10% in vital capacities and 10 20% in maximal breathing capacities following the administration of each of these three preparations Excellent clinical results were obtained in patients with mild to moderate bronchospasm but the drugs failed to relieve symptoms of severe intractable asthma

Adverse side reactions to all four drugs tested were minimal Cardalin in doses as high as 600 mg was well tolerated and caused comparatively little gastrointestinal disturbance

Study of plasma theophylline levels revealed appreciable concentrations of theophylline in the circulating blood as long as seven hours after administration of 300 and 600 mg cardalin

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PULMONARY MYCOSES

Occurrence of Histoplasmosis in Epidemics Etiologic Studies of 13 epidemics were made by Michael L Furcolow and J Thomas Grayston (Univ of Kansas) A strikingly consistent symptom complex accompanied the illnesses in all of the epidemics Typically onset was sudden with general

(1) A n. Alle gy 11 301 312 M y J 1953
(2) Am R T be 68 307 3 0 Septembe 1953

usual pulmonary disease provide convincing evidence that these were epidemics of acute histoplasmosis —Ed]

Endobronchial Lesions in Pulmonary Blastomycosis Wilson Weisel and Francis B Landis[3] (Marquette Univ) report *seven cases of pulmonary blastomycosis due to Blastomyces* dermatitidis in which endobronchial lesions were seen during the acute phase The commonest lesion was superficial ulceration associated with a characteristic secretion in the bronchi The granulomatous character of the lesion however was demonstrated by the appearance of an endobronchial mass The infecting organisms were first discovered in secretions collected during bronchoscopy Radiologic features included exudative diffuse disease lobar atelectasis cavity formation and pleural involvement with effusion In the quiescent or healing phase fibrotic strandlike residues were most common

The clinical course was uniformly favorable Because the lesions were endobronchial iodine was administered in the form of aerosolized ethyl iodide This caused dramatic and pronounced improvement of symptoms and radiologic appearance of the pulmonary lesions It was evident in all patients that the infection was systemic not a localized pulmonary process The finding of the organism in the tissues was apparently the only distinguishing feature in one of the two resected specimens which could help in differentiating the process from other granulomatous lesions and it was also characteristic in the examination of biopsies from skin lesions

[Stilbamidine is usually more successful than the iodides in systemic blastomycosis (see next article) —Ed]

Stilbamidine in Treatment of Disseminated Blastomycosis Report of Two Cases is presented by C R Cummins B Bairstow and Lyle A Baker[4] (V A Hosp Hines Ill)

CASE 1 —Man 39 was hospitalized with right upper lobe pneumonia and was treated with antibiotics and potassium iodide for three months Because resolution of the infiltration was so slow lobectomy was performed Pathologic diagnosis was chronic fibrosing pneumonitis with foreign body granulomas

He was readmitted 11 months after discharge because of skin lesions Biopsy disclosed Blastomyces dermatitidis On review this organism was also found in the lung sections The chest x ray disclosed elevation of the right diaphragm there was no pulmonary infiltration Liver function test showed parenchymal damage no specific cause could be found There were no other signs of the

(3) J Th S g 25 570 581 J 1953
(4) A M A A b I t M d 92 98 107 July 1953

Of the 116 patients involved in 11 epidemics 94 given skin tests all reacted positively to histoplasmin Only a small percentage reacted to tuberculin coccidioidin or blastomycin Prevalence of histoplasmin sensitivity in the general population which should be taken into account in evaluating the significance of the 100% prevalence in this series is shown in Figure 37 Most persons involved in epidemics were residents of the area in which the outbreaks occurred Nearly all persons involved in two army camp epidemics were from states of low histoplasmin sensitivity In addition conversion of reactions to histoplasmin skin tests from negative to positive which is evidence of recent histoplasma infection was demonstrated in three children one to two weeks after onset of illness

All but 1 of 54 serums obtained within three months after onset of the epidemic reacted at least in a low titer and 44 caused definitely positive reactions As time elapsed after infection the high titers decreased and the percentage of doubtful and negative reactions rose Significant falls in titer with time were demonstrated in many persons The authors experience has confirmed the previously reported specificity of these serologic reactions

The tendency of pulmonary histoplasmosis to heal with calcification has been frequently demonstrated The disseminated miliary type of calcification has been particularly associated with histoplasmosis Of the 63 persons with some type of calcification 44 had disseminated miliary calcification and the rest had single or multiple lesions Only 12 of the 73 persons followed at least four years did not have calcification

Examinations of soil samples collected at and around the point sources of the epidemics yielded H capsulatum in 11 of the 13 outbreaks The isolations were from samples collected at the exact point source except in four instances where the samples were collected from nearby locations

Except in one infant who died of histoplasmosis the fungus was not isolated from patients in this series Proof of the nature of the etiology of these epidemics is therefore somewhat indirect but the occurrence of groups of cases with similar reactions makes this type of etiologic evidence secure

[The etiologic studies here reported on the interesting series of epidemics known by such diverse names as cave sickness acute miliary pneumonitis granulomatous pneumonitis angleworm pneumonia and un

grade exudative bronchitis with fungi which morphologically re sembled geotrichum Cultures were positive for geotrichum He was treated with sodium iodide intravenously and potassium iodide orally Two weeks later he no longer had hemoptysis and little coughing Except for one sudden episode in December 1952 when he coughed up a cupful of bright red blood he had no symptoms A bronchogram was negative Bronchoscopy with cultures of sputum failed to reveal recurrence of the fungous infection

CASE 2—Man 54 had been hospitalized numerous times for hypertensive and arteriosclerotic heart disease with episodes of cardiac insufficiency On his last admission acute pulmonary edema was present He had a red atrophic tongue and a cough productive of brownish red sputum which was extremely tenacious mucoid and odorless Spores of geotrichum were found in sputum smears Sputum cultures revealed luxuriant growths of geotrichum Chest x rays showed no parenchymal disease He was treated with potassium iodide orally and within a few days the putum lost its rusty color became more abundant and was less mucoid Within three weeks the cough subsided and attempts to obtain geotrichum on smear and culture were unsuccessful He died a few weeks later with left ventricular failure and autopsy failed to reveal any endo bronchial or pulmonary di ease

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TUBERCULOSIS

Role of Perforation of Hilar Lymph Nodes into Bronchial Tree of Adults According to H Iselin and F Suter[6] (Davos Platz Switzerland) postprimary tuberculous hilar lymph node perforation in adults is not rare Bronchoscopy on 1 228 tuberculous adults revealed its presence in 38 and residues of such perforation in 81 others Almost 70% of the patients were aged 18 30 and the majority were women Symptoms do not aid in diagnosis only two patients expelled suspicious ma terial and once it was necessary to remove a calcareous body in connection with a perforation into the bronchus of the mediobasal segment of the right lower lobe In some cases the sputum suddenly became positive but generally it was some pulmonary change that suggested the perforation

Perforation of tuberculous hilar lymph nodes into the bronchial tree with bronchogenic dissemination can lead to tuberculosis of the lung The perforation together with localized destruction of the ciliated epithelium and mucous membrane and stenosis is followed by disturbances of venti

(6) D Ch t 25 30 311 M h 1954

disseminated blastomycosis Dermatologic lesions remained stationary on treatment with antibiotics iodides and moist compresses Consequently he was treated with a total of 2 4 Gm stilbamidine intravenously The lesions rapidly cleared Potassium iodide therapy was continued Three months after discharge he had gained about 90 lb The skin lesions were well healed General sense of well being and health were excellent

CASE 2—Man 49 had osteomyelitis of the right foot which progressed so rapidly that a below knee amputation was performed about one month after onset of symptoms The sections disclosed B dermatitidis One month later he was hospitalized for complete urinary retention Blastomyces dermatitidis was found in the initial prostatic smear Chest x ray showed a coarse granular type of infiltration bilaterally the organisms were not recovered in the sputum Shortly thereafter he became febrile and had multiple cutaneous abscesses A course of 2 12 Gm stilbamidine was followed by subsidence of all symptoms and a surprising weight gain The skin lesions cleared gradually and after four weeks no lesions were apparent Chest x ray showed improvement

Three weeks after discontinuance of treatment urinary retention recurred Smear and culture were positive for B dermatitidis There was no fever or generalized symptoms but he was given another course of stilbamidine (total 1 8 Gm) No signs of drug toxicity developed Liver and renal function remained unimpaired Six months later he was in good physical condition and had gained approximately 40 lb The multiple subcutaneous lesions were well healed Prostatic smear was negative for blastomycosis

These results were gratifying when compared to previously unsatisfactory treatment of this disease Both patients had definite but transient toxic neuropathy involving the fifth nerve which was mild and insignificant in view of the clinical improvement Neuropathy always occurs if large doses of stilbamidine are given

[The treatment of systemic blastomycosis with stilbamidine introduced by Schoenbach and his associates in 1951 has been strikingly successful but the fifth cranial nerve damage has been troublesome Snapper and McVey (Am J Med 15 603 1953) have used 2 hydroxystilbamidine which is less toxic Whether the therapeutic results are as well sustained as with stilbamidine is not yet certain—Ed]

Endobronchial Geotrichosis Richard Minton Rodolfo V Young and Edward Shanbrom[5] (Gorgas Hosp Ancon C Z) present two cases

CASE 1—Man 53 was hospitalized for hemoptysis in 1946 and for cough and hemoptysis accompanied by weakness and slight pyrexia in 1950 There were no positive physical findings Bronchoscopy showed normal main stem bronchi with hyperemic mucosa and white exudative patches that bled easily Biopsies revealed low

(5) Ann I t Med 40 340-343 F brua y 1954

accompanying tuberculous disease of bronchus and lung The treachery of such blocked cavities is well known but they are also a method of healing Their development is common in the lung under a pneumothorax and usually has a favorable outcome The round foci of the second type have often been classified according to their size but the authors feel that this is of no value These foci may get smaller and heal with calcification they may persist unchanged for years they may grow through development of successive layers of encircling granulation tissue or they may multiply While the accompanying lung disease resolves the round focus may develop While some round foci shrink and calcify others may grow They may involve the bronchus and they may cavitate Cavitation may be accompanied by spread of the parenchymal disease but this is by no means always the outcome

Too ready acceptance of the thesis that the round focus is responsible for spread of disease is unwise All patients with tuberculous disease are liable to breakdown The round and apparently solitary focus is so frequently accompanied by other tuberculous foci in the lung that these radiologically invisible lesions may well be the source of bacilli A round focus which has recently developed by encapsulation of a large area of consolidation is probably a greater risk than the other more common type The treacherous reputation of round foci is due largely to imperfect knowledge of their natural history Although the various patterns of behavior are known their relative frequency is still unknown The following case is of interest in that both types of round foci developed in the same patient

Woman 23 had extensive tuberculous infiltration in left lung which healed after a left artificial pneumothorax was induced and maintained from 1946 to 1949 A tuberculous lesion was first noted on the right (radiologically astride the transverse fissure) in February 1946 and by February 1947 it had developed into a large lesion with a central 2 cm tension cavity At that time a lesion had developed under the cartilage of the first rib to a diameter of 1 5 cm The picture in June showed that the cavity had blocked being now opaque and 1 5 cm in diameter The focus by the first rib had not enlarged and there were several flecks of calcium By September 1948 the upper focus on the right had further enlarged to 2 5 cm diameter with a 0 5 cm. central radiolucency whereas the midzone focus had remained unchanged Slow growth of the upper focus continued and by August 1950 it was over 3 cm in diameter with

lation and drainage Thus pulmonary tuberculous foci are easily formed by the spread of secreted material from the caseous lymph nodes The fistula from the lymph nodes into the bronchus may not be readily seen on bronchoscopy The bronchus may show granulation tissue immediately after perforation and later may become scarred

The logical treatment is rest for several months during which the function of the bronchus must be stimulated by active cough Expectorants may be of help Drainage must be aided by aspiration and shinking of the bronchus endoscopically Streptomycin PAS as well as isonicotinic acid hydrazide are beneficial Only in extreme cases should granulation be removed since the repeated action of forceps cautery and caustics injures the functionally important remaining ciliated epithelium

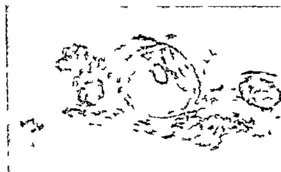
[This report lends clinical support to the claims of Schwartz (see 1953 54 YEAR BOOK pp 130 134) and others based on autopsy findings relative to the frequency of lymph node perforation in adults The significance of this mechanism as a comparatively frequent cause of bronchogenic spread in the pathogenesis of adult pulmonary tuberculosis is not yet widely accepted It should perhaps be taken into greater account with regard particularly to the selection of patients for pulmonary resection Some of the failures and relapses after surgery may be attributable to this cause —Ed]

Some Observations on Historical Appreciation, Pathologic Development and Behavior of Round Tuberculous Foci are presented by *W M Macleod and A Taid Smith*[7] *(St Thomas s Hosp London)* In 14 patients 8 of whom were operated on two categories of lesions were seen (1) those at a stage in the history of a cavity in which the draining bronchus had become occluded the air absorbed and the walls contracted around the remaining caseous contents and (2) those in which masses of tissue had been sealed from the outset and through the greater part of their life history showed less tendency to undergo the extensive softening and cavitation which is the fate of many tuberculous lesions in the lung These lesions are the result of progressive but fluctuating centrifugal growth of tuberculous granulation tissue which undergoes necrosis and may become caseous or even liquefied The factors responsible for these changes are largely unknown

The behavior of blocked cavities must be influenced by many factors including the nature of the cavity itself and the

(7) Thora 7 334-353 December 1952

tissue infiltrated by lymphocytes and with an occasional hard tubercle Many similar noncaseous tubercles were present in the surrounding lung and bronchi (Fig 40) The central mass was necrotic but its structure was largely conserved and demonstrated by silver impregnation It consisted of concentric zones of ghost tuberculous granulation tissue and pigmented lamellar fibrous tissue The central part was largely liquefied but the remaining parts showed the characteristics of a conglomeration of hard tubercles The nodule from the lower lobe consisted of amorphous caseous material con



Fg 40—S ct h w g tell t od l C tral h l l m n f b on h (C rt y f M l d W M d Sm th A T Th 7 334 353 Decemb 195)

taining many acid fa t bacilli encapsulated by a zone of dense fibrous tissue The surrounding lung contained discrete hard tu bercles

Present Chaos Regarding Resection of Residual Caseous Lesions in Pulmonary Tuberculosis According to Edward J O Brien (Detroit) Arthur C Miller (Loma Linda Calif) Paul T Chapman Koert Koster and Paul V O Rourke[8] (Detroit) it is generally conceded that the pathogenicity of tubercle bacilli may be affected by their accommodation to incarceration within the necrotic lesion Acid fast bacilli can be recovered from many of these lesions in smears and cul tures especially from open cavernous lesions However whether many of these bacilli are virulent is unfortunately still controvers al

The contribution of Medlar *et al* regarding the residual caseous lesion and simple excision was based on theory not on proved evidence It is unfortunate that further research

(8) J Th S g 26 441-446 N mbe 1953

a 1 5 cm central trinslucency Bronchoscopy showed no evidence of bronchial tuberculosis On October 22 the posterior segment was removed without difficulty The midzone lesion was removed locally from the apex of the lower lobe The immediate postoperative course was uneventful 30 Gm streptomycin having been given She was well until March 1951 when there was further spread of the disease in the right upper lobe with positive sputum

The excised posterior segment contained associated with the



F g 38 (l ft) —S t on f l g r d focu sh w g t rrupt n of bro h p o m l a d d t) to th l
F g 39 (ght) —La g d focu h ws w ll t l m ated n t e w th l q fi d cente Two ne ghbo g foc n be een add t t a sect n of r l t d b on h
(C tesy f M l od W M a d Sm th A T Thora 7 334 353 D c mb 195)

segmental bronchus a partly caseous ovoid yellow nodule The segmental bronchus was incorporated and destroyed in the edge of the lesion (Fig 38) An irregular long narrow cavity had formed in the center of the ca cou material The rest of the necrotic tissue had an appearance of concentric laminae of thin pigmented zones and wider yellow zones (Fig 39) Two small yellow outlying nodules were present. A second small piece of lung from the lower lobe contained a spherical well encapsulated mass of caseous ma terial

Microscopic examination howed a peripheral thin zone of fibrous

much smaller with walls so thin they are difficult to see these lesions can be expected to close and heal with some form of collapse therapy Unfortunately these methods have been virtually discarded although many thousands of patients have recovered and remained well after such treatment

The argument for widespread resection is that the patient s future would be less hazardous if all lesions including nubbins were removed However a patient is better off with no surgery at all if he does not need it Deaths do occur from resection as do bronchopleural fistulas remaining lobes that fail to re expand sufficiently empyema added thoracoplasty Schede operations as well as early and late exacerbations of disease The percentage of such occurrences is small but it is 100% in those affected

Frequently more disease is found at operation than was apparent in the x rays Areas of so called satellites often surround the nubbin and other infiltrations not suspected preoperatively show evidence of previous disease After long chemotherapy the former are seldom seen These areas rather than the nubbin itself may actually be the cause of reactivations after cessation of treatment The surgeon does not remove all disease by wedges segments or lobes if disease has existed elsewhere previously Scars or nubbins are present in many people who have been living normal lives for years Resection is not necessary unless reactivation occurs

[Amen !—Ed]

Extraperiosteal Lucite Ball Plombage Single stage extraperiosteal lucite ball plombage has proved to be a simple and safe substitute for multistage thoracoplasty in pulmonary *tuberculosis In addition because pulmonary function is* spared it can be applied to advanced bilateral disease in patients in the older age group who have significant amounts of cavitation emphysema fibrosis or other impairments

Francis M Woods and Louis Buente[9] (Tufts College) report results of 285 procedures on 227 patients with unilateral and 43 with bilateral disease Conversion of sputum followed the procedure in 149 (72%) patients with unilateral and 6 (16%) with bilateral involvement In 26 others (13%) with unilateral and 18 (47%) with bilateral disease sputum conversion occurred after an additional procedure such as

(9) Am R T b c. 68 902 911 D mb 1953

was not done before surgeons began reckless cutting There is a wide divergence of opinion regarding which lesions to resect There seems to be no disagreement that open cavities *are potentially most dangerous Auerbach has shown that* under chemotherapy re epithelization occurs at the broncho cavitary junction and often extends some distance into the cavity wall itself The tubercle bacillus is aerobic and a patent bronchial junction adds to the difficulty of causing the organism to die

Medlar states that bacilli in closed cavities are apparently avirulent because of their physiochemical environment but he believes they are temporarily dormant and not dead DuBos states that long chain fatty acids are powerful antimicrobial agents which are released during necrosis by lipolytic en zymes with resulting caseous material Before chemotherapy it was thought that cavity closure and healing resulted after the bronchial opening became occluded rendering the closed inspissated material more susceptible to the physiochemical environment That more cavities are filled after chemotherapy is unquestionable but this is difficult to correlate with Auer bach s findings Some believe that chemotherapy especially isoniazid dries up the material and prevents its expulsion Many relapses or extensions of disease before chemotherapy obviously came from expelled caseous foci but now this is not apparent In a large percentage of patients reactivation seems to occur in other lesions which existed previously

Treatment of the small nodular apparently arrested resi due (nubbin) present after one or more years of medical man agement is controversial It seems incongruous to treat a hos pitalized patient for 12 18 months or more watch the lesion clear from an extensive infiltration to a nubbin that has re mained stationary for months (with negative sputum for a year or more), then debate whether to send him home or resect

It has been the authors opinion that noncavernous lesions with somewhat extensively mixed residues after long chemo-therapy and little or no change in x ray appearance should be resected They have no proof now however from bacterio logic studies that even this is correct Many believe that thick walled cavities should be resected early but cavity walls thin out markedly under chemotherapy and often become

late complications appeared in 11 with unilateral and 2 with bilateral lesions There were no postoperative deaths among the patients with unilateral and 2 (4 6%) such deaths among those with bilateral disease

The following case represents one of the extreme cases of bilateral disease which responded to this approach

Woman 22 in August 1951 had far advanced bilateral pulmonary tuberculosis with large cavities present in each apex (Fig 41) Both sputum and urine were positive for acid fast bacilli Long term streptomycin and PAS therapy was started A six rib left extra periosteal plombage was done on September 26 and a five rib right extraperiosteal plombage on November 16 (Fig 42) After a long rest and chemotherapy sputum and urine became consistently negative for tubercle bacilli on culture The patient was receiving no chemotherapy and was doing light work 18 months after the second operation

[This type of procedure is to an increasing extent displacing the conventional thoracoplasty in cases unsuitable for resection Plastic materials other than Lucite balls have also been used successfully The most important difference however from the older largely unsatisfactory procedures of this type is the stripping of periosteum from the overlying ribs An additional layer of tissue consisting of the periosteal beds and the intercostal bundles is thus interposed between the collapsed lung and the plombe By leaving the denuded ribs the chest wall remains stable postoperatively which gives this procedure a material advantage over thoracoplasty in poor risk patients Regeneration of bone in the displaced periosteal layer later establishes essentially the same conditions as a thoracoplasty The plombe and the denuded ribs can be subsequently removed if infection or other complications develop but this has been rarely necessary In addition to its advantages in safety and the sparing of function this ingenious operation results in no appreciable deformity Still longer follow up data are needed before its place i entirely secured but this report is extremely encouraging —Ed]

Comparative Study of Streptomycin and Dihydrostreptomycin in Pulmonary Tuberculosis Sumner S Cohen Lynn Johnsen M R Lichtenstein and William J Lynch[1] report on 294 patients from four tuberculosis hospitals who received 1 Gm streptomycin or dihydrostreptomycin in a single intramuscular injection per day plus 12 Gm para aminosalicylic acid (PAS) given orally in divided doses Both streptomycin and dihydrostreptomycin were valuable in amenable forms of tuberculosis and it was not possible to determine any significant difference in their therapeutic efficacy When administered with PAS (or one of its salts) neither form of streptomycin was associated with significant emergence of drug resistant infections

(1) Am. Rev T b c 68 2 9 37 A gust 1953

lobectomy or a second course of antimicrobial agents The anticipated erosions migration of spheres and infections around the plastic material did not occur Fluid developed



F g 41 (bove) —R ght a d l ft l g h w ng l ge b late al ca t
F g 42 (l ft) —O y ft b l t l t ape t l plombag N t pa t al d m ne l at n of d d d bs
(Court y of Wood F M a d B t L Am Re T be c 68 90 911 Dec mbe 1953)

around the material in the first postoperative days but only an average of one aspiration per operation was necessary Tuberculous complications such as spreads exacerbations empyemas and chest wall infections occurred postoperatively in 2 patients with unilateral and 3 with bilateral disease and

streptomycin or dihydrostreptomycin was 20 mg /kg daily No difference in the therapeutic efficacy of the two drugs was discernible when results were evaluated after the drugs were given for 120 days

No significant difference was observed in frequency of drug resistant strains of tubercle bacilli which was less than 8% with either drug The small percentage of patients in each original group who still had sputum positive for tubercle bacilli after one year of treatment emphasizes the impropriety of drawing any conclusions about the drug resistance studies with respect to the two drugs

Vestibular disturbances can occur with either drug but are more frequent more severe and often occur earlier with streptomycin than with dihydrostreptomycin Auditory disturbances are relatively uncommon with streptomycin and when present are usually less severe Auditory disturbances are more to be expected with dihydrostreptomycin They are usually mild when the drug is given for only 120 days They are more severe and more frequent when administration is prolonged beyond six months Auditory disturbances can progress even after therapy is stopped or they may appear some time after the conclusion of chemotherapy The earliest changes of ototoxicity detected with either drug are usually tinnitus and/or mild high tone loss

Peripheral Neuropathy in Tuberculosis Patients Treated with Isoniazid Although peripheral neuropathy was not found in a large number of tuberculous patients who received 50 100 mg isoniazid three times daily it was noted by Harold N Lubing[3] (V A Hosp Madison Wis) in six patients given 100 150 mg three times daily (3 9 9 2 mg /kg) Five patients had far advanced pulmonary tuberculosis All were chronically ill toxic and emaciated Within 6 weeks to 11 months after initiation of isoniazid therapy they complained of pain and paresthesia in the extremities Neurologic findings included weakness in the muscles of the hands impaired dorsiflexion of the feet diminished sensory modalities such as light touch vibratory and position sense and reduction or absence of deep reflexes particularly the knee and ankle jerks Isoniazid was discontinued at least temporarily in most cases and symptoms and signs slowly abated Reinstitution of the

(3) Am R T bc 68 458 461 S pt mb 1953

Vestibular toxicity which generally occurred relatively early in the course of treatment was more frequently encountered with streptomycin Auditory toxicity which tended to occur later was more frequently due to dihydrostreptomycin Although usually ranging from subclinical to moderate in degree the auditory disturbance can be serious It can be progressive or may appear belatedly after chemotherapy has been discontinued High tone (audiometric) loss or complaint of sustained high pitched tinnitus may be the first indication of trouble and should always be considered significant

[The principal significance of this and of the related study by Mahady *et al* (following article) concerns the observations on auditory and vestibular toxicity Both studies confirm earlier reports that serious auditory disturbances from prolonged administration of dihydrostreptomycin in 1 0 Gm daily dosage are comparatively frequent Moreover the hearing loss may be progressive even after discontinuance of the therapy Streptomycin is therefore the preferred drug in tuberculosis despite its greater vestibular toxicity Vestibular damage is less serious in disabling consequences than auditory but it should be held to a minimum by not exceeding the dosage of 1 0 Gm daily Earlier experience with larger doses resulted in practically 100% of severe vestibular disturbances whereas with present dosage the damage in most instances falls into the slight or moderate categories Whether the mixture of streptomycin 0 5 Gm with dihydrostreptomycin 0 5 Gm introduced by Hobson will provide the ideal preparation is not yet established in the published literature though observations on patients treated for 120 days seemed favorable (Heck and Hinshaw Tr 12th Conf Chemotherap Tuberc Veterans Administration Army and Navy 1953 pp 291 and 294) The crucial observations will be after a year or more of continued administration These are said to be favorable but detailed reports are not yet available

The low frequency in both of the present studies of drug resistant strains at 120 days should not be interpreted as indicating that combined streptomycin (or dihydrostreptomycin) and PAS administration eliminates the problem of streptomycin resistance in long term therapy In a U S P H S study of bacterial resistance (1953 54 YEAR BOOK pp 207 209) it was found that at the end of six months of streptomycin in combined treatment with either isoniazid or PAS all cultures *still positive* for Mycobacterium tuberculosis had lost some measure of their initial susceptibility to streptomycin and to both streptomycin and isoniazid when these were both given Tests for PAS susceptibility are not often made but PAS resistance is also a factor of importance in prolonged therapy —Ed]

Comparative Study of Streptomycin and Dihydrostreptomycin in Pulmonary Tuberculosis Stephen C F Mahady Frank L Armstrong Frederick Beck Ralph Horton and N Stanley Lincoln report the results of a study conducted in four New York State tuberculosis hospitals The dosage of

(2) Am Rev T berc. 68 38 48 A g st 1953

mycin isoniazid and 5% of those receiving isoniazid alone had cultures positive for tubercle bacilli at the 40th week. On all regimens the proportion of patients with temperatures above 99 F decreased greatly during treatment. The decrease was greatest among those receiving streptomycin isoniazid. All three regimens were about equal with respect to gain in body weight for patients who were at least 10% underweight at the beginning of treatment.

Patients receiving streptomycin isoniazid maintained a small but consistent advantage. Improvement discernible on roentgenograms continued throughout treatment although at a slower rate during the later weeks.

[This fourth report of the United States Public Health Service Cooperative Investigation is of particular interest because this is the only one of the large control studies in which the regiment of *isoniazid alone* was continued for a period exceeding *six* months. In the Veterans Administration, Army and Navy studies and in the British studies of the Medical Research Council isoniazid alone was dropped because of the in vitro evidence of bacterial resistance noted relatively early in the course of treatment. The experience in miliary tuberculosis reported by the Cornell group (see 1953-54 YEAR BOOK pp. 196-199) had shown however that early relapse under treatment with isoniazid is not common if it occurs at all. Relapse of miliary tuberculosis in contrast, is frequent under streptomycin when this is given alone. The inference may be drawn from this that isoniazid resistance in terms of *neutralization of therapeutic effect* does not necessarily proceed as rapidly as might be anticipated from in vitro tests of cultures derived from pulmonary tuberculosis patients whose sputum remained unconverted. In the present study it is found that, contrary to the expectations of many in pulmonary tuberculosis also the assessment of isoniazid *in clinical terms* shows it to be approximately equal up to the nine month point, to streptomycin PAS. The relatively slight superiority of streptomycin isoniazid over both isoniazid alone and streptomycin PAS may be attributable to an actual enhancement of each other by streptomycin and isoniazid. Against the apparent advantage however of this combination must be balanced the risk of eventual bacterial resistance to both drugs. In the case of streptomycin at least, a significant correlation is well established between resistance demonstrated in vitro and loss of therapeutic efficacy. In the case of isoniazid the correlation between these factors is less well established and significant drug resistance may develop less rapidly than the conventional methods of testing appear to indicate. It would be unwise however to assume that significant resistance to isoniazid does not occur eventually. The question of *what is the treatment of choice in pulmonary tuberculosis* is thus not answered by this study but it may be reasonably inferred from these results that such is *not* streptomycin PAS which up to now has been most frequently recommended. For if isoniazid as one, and streptomycin PAS as another are to be used independently as separate regimens in order to avoid compromising both of the major drugs simultaneously by administering them concurrently the initial choice appears more advantageously to be isoniazid on considerations of cost, ease of administration and tolerance.

A later study by the same co-operative group follows on comparisons

drug usually was followed by exacerbation of symptoms

Vitamin B_1 in both moderate and massive doses did not appear to modify the rate of improvement Likewise nicotinic acid vitamin B and vitamin B complex had no significant effect on intensity of symptoms

[Peripheral neuropathy from isoniazid is infrequent, even with continuous therapy for a year or longer when the total daily dose does not exceed 5 mg /kg body weight With very large doses (16 24 mg /kg /day) the incidence is as high as 37% (Biehl and Skavlem Am Rev Tuberc. 68 296 1953) An incidence of 3 4% is reported at the 10 mg./kg level (U S Public Health Service Co operative Investigation of Antimicrobial Therapy of Tuberculosis Am Rev Tuberc 69 1 1954) —Ed.]

Control Study of Comparative Efficacy of Isoniazid, Streptomycin-Isoniazid and Streptomycin Para Aminosalicylic Acid in Pulmonary Tuberculosis Therapy IV Report on 40 Week Observations on 583 Patients with Streptomycin susceptible Infections Frank W Mount Barbara E Jenkins and Shirley H Ferebee[4] (U S P H S) gave 183 patients streptomycin plus PAS 195 streptomycin plus isoniazid and 205 only isoniazid At the beginning of treatment the characteristics of the patients and their disease were similar in the three groups Nearly two thirds (63%) had advanced cavitary disease one third (33%) advanced disease without cavitation and only a few (4%) had minimal involvement

During the 40 weeks 13 patients died of tuberculosis 5 had received *streptomycin PAS* 4 *streptomycin isoniazid* and 4 isoniazid

By the 40th week some improvement was observed in the films of 78% of the streptomycin isoniazid group 71% of the streptomycin PAS patients and 70% of the isoniazid patients When significant improvement was restricted to marked and moderate the streptomycin isoniazid group showed a slight but consistent superiority throughout treatment whereas no difference was discernible between the other two groups If slight deterioration is disregarded only 7% of the streptomycin PAS and isoniazid groups and 5% of the streptomycin isoniazid group grew worse

At the end of treatment sputum cultures positive for tubercle bacilli were obtained from approximately two tenths of the streptomycin isoniazid group and from approximately three tenths of the patients on the other two regimens Among patients who e cultures were negative at 28 weeks 6% of those receiving streptomycin PAS 4% of those receiving strepto

(4) Am Re T berc. 68 264 269 A gust 1953

mycin isoniazid and 5% of those receiving isoniazid alone had cultures positive for tubercle bacilli at the 40th week On all regimens the proportion of patients with temperatures above 99 F decreased greatly during treatment The decrease was greatest among those receiving streptomycin isoniazid All three regimens were about equal with respect to gain in body weight for patients who were at least 10% underweight at the beginning of treatment

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A later-study by the same co-operative group follows on comparisons

between isoniazid streptomycin isoniazid PAS and isoniazid streptomycin PAS The results are of a preliminary nature but they open further possibilities in choice of therapy The optimal regimen may in the final assessment prove to be not necessarily one and the same for all types and varieties of pulmonary tuberculosis —Ed]

Progress Report on Therapeutic and Toxic Effects of Combinations of Isoniazid, Streptomycin and Para aminosalicylic Acid is presented by the United States Public Health Service Co operative Investigation of Antimicrobial Therapy of Tuberculosis[5] From study of more than 1 600 patients with pulmonary tuberculosis preliminary results of chemotherapy are presented for the 461 patients who have been under observation longest By random allocation the patients were assigned to five treatment regimens (1) 3 mg isoniazid/kg plus streptomycin in 91 (2) 3 mg isoniazid/kg plus PAS in 85 (3) 10 mg isoniazid/kg plus streptomycin in 95 (4) 10 mg isoniazid/kg plus PAS in 102 and (5) 10 mg isoniazid/kg plus streptomycin plus PAS in 88 The study was designed to compare PAS and streptomycin as partners for isoniazid to evaluate the simultaneous use of all three drugs and to determine the effect of increasing isoniazid dosage

The patients were followed for 20 weeks of treatment The therapeutic effect was measured by roentgen clinical and bacteriologic comparison of the different regimens Tentative results indicate that isoniazid plus PAS is as effective as isoniazid plus streptomycin that simultaneous use of all three drugs does not excel the combination of either isoniazid and streptomycin or isoniazid and PAS and that although the therapeutic effectiveness of isoniazid does not increase with increased dosage toxic reactions are much more common with the higher dose

These preliminary results must be interpreted with caution because they are based on groups of only moderate size and on only limited observation

Isoniazid in Combination with Streptomycin or with PAS in Treatment of Pulmonary Tuberculosis Fifth Report to Medical Research Council by Tuberculosis Chemotherapy Trials Committee[6] The 391 patients studied included those with acute rapidly progressive disease of recent origin (group 1) other forms considered suitable for chemotherapy (group 2) and chronic disease considered unlikely to respond to

(5) Am R Tuberc 69 1 12 J ry 1954
(6) Brit M J 2 1005 1014 N v 17 1955

chemotherapy (group 3) The principal comparison was made between the patients in groups 1 and 2 on 1 Gm streptomycin daily plus 200 mg isoniazid daily (SH) and those on 20 Gm PAS (sodium) daily plus 200 mg isoniazid daily (20 PH) On admission there was a similar distribution of patients with severe and less severe illness in the two treatment series At the end of three months the general condition had improved in 89% of the SH patients and 88% of the 20 PH patients Average weight gain fall in sedimentation rate incidence of temperature normalization radiographic and bacteriologic improvement did not differ significantly in the e two series

Bacillary resistance to isoniazid was found in 2 of 39 SH patients with positive cultures tested at three months compared with none of 29 similar 20 PH patients Bacillary resistance to streptomycin was found in 1 of 38 culture positive SH patients and to PAS in 1 of 28 similar 20 PH patients

On the basis solely of results at three months it was concluded that the PAS isoniazid combination is effective clinically and bacteriologically ranking with the most efficacious treatments so far studied namely 1 Gm streptomycin daily plus 200 mg isoniazid daily and 1 Gm streptomycin daily plus 20 Gm PAS (sodium) daily

[As pointed out last year the British regimen of streptomycin PAS is more intensive with respect to dosage of both drugs than the regimen commonly employed in the United States From the successive reports of the British studies it appears that the more intensive streptomycin PAS regimen is also a clinically somewhat more effective one The British reports consistently rank streptomycin PAS as equal with isoniazid streptomycin and superior to isoniazid alone whereas in the U S Public Health Service Co-operative Investigation (p 186) streptomycin PAS ranks only with isoniazid and below isoniazid streptomycin in clinical results

Much of the current interest in trials of streptomycin and of PAS as *companion drugs to isoniazid* is predicated on the assumption that isoniazid administered alone is not effective except for relatively short periods This assumption is based in largest part not on clinical evidence but on *laboratory* observations such as those reported in the following article — Ed]

Emergence of Bacterial Resistance in Pulmonary Tuberculosis under Treatment with Isoniazid, Streptomycin Plus PAS and Streptomycin Plus Isoniazid A report by the Laboratory Subcommittee of the Tuberculosis Chemotherapy Trials Committee Medical Research Council[7] is presented on 264 patients treated with isoniazid alone 233 with streptomycin plus PAS

(7) La t 2 217 2 3 A g 1 1953

between isoniazid streptomycin isoniazid PAS and isoniazid streptomycin PAS The results are of a preliminary nature but they open further possibilities in choice of therapy The optimal regimen may in the final assessment prove to be not necessarily one and the same for all types and varieties of pulmonary tuberculosis —Ed.]

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The patients were followed for 20 weeks of treatment The therapeutic effect was measured by roentgen clinical and bacteriologic comparison of the different regimens Tentative results indicate that isoniazid plus PAS is as effective as isoniazid plus streptomycin that simultaneous use of all three drugs does not excel the combination of either isoniazid and streptomycin or isoniazid and PAS and that although the therapeutic effectiveness of isoniazid does not increase with increased dosage toxic reactions are much more common with the higher dose

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(5) Am R T b c. 69 1 12 J ry 1954
(6) B t M J 2 1005 1014 N 17 1953

and by the 14th week 80% of the group yielded cultures showing increased resistance in vitro Loss of drug effect as indicated by reversion of sputum bacillary counts to previous high levels or by unfavorable radiographic changes occurred during therapy in 28 patients In most cases such an event was preceded by or coincided with the appearance of drug resistant organisms in the sputum Results in these cases suggested that the appearance in the sputum of bacilli with only slight degrees of increased drug resistance may be associated with roentgen or bacteriologic evidence of loss of drug effect

General clinical improvement which was striking in most cases was often maintained despite radiographic or bacteriologic deterioration In this type of case these drugs may be of use in conjunction with collapse or excision of cavitary disease and in combination with other chemotherapeutic agents

[The authors base their conclusion that the deteriorations are attributable to the emergence of drug resistant organisms on their correlations which showed a coincident change of some degree in sensitivity status in 23 (83%) of 28 instances Inspection of the data shows however that in 13 or nearly half of the deteriorations the cultures were sensitive or resistance was *slight* (0 2 μg /ml[8] in the case of isoniazid) In 21 or three-quarters resistance was *intermediate* (1 0 μg in the case of isoniazid) or less Higher levels than these are attained during therapy in plasma, body fluids and tissues The correlations thus considered are less satisfactory and do not readily explain the extraordinarily high incidence of deteriorations here observed If the changes in bacillary content of sputum are disregarded and only the roentgen deteriorations considered there are reported 23 instances of roentgenographic relapse in 41 patients or more than half during the first 16 weeks of therapy This is in marked contrast to the experience of others including our own and that of the United States Public Health Service Co-operative Investigation (p 186) In long term therapy for 9 months (U S P H S study) and for 12 months (Cornell study Am Rev Tuberc August, 1954) only 7 7 and 12 8% of patients respectively had roentgenographic deterioration —Ed]

Study of Virulence of Isoniazid Resistant Tubercle Bacilli in Guinea Pigs and Mice Preliminary Report W C Morse O L Weiser D M Kuhns M Fusillo M C Dail and J R Evans[9] report two independent experiments on the animal virulence of isoniazid resistant tubercle bacilli conducted at Walter Reed Army Medical Center and Fitzsimons Army Hospital In the first experiment acid fast isoniazid susceptible bacilli culturally identified as Mycobacterium tuberculosis and determined to be pathogenic for the guinea pig were transferred from Lowenstein medium free from isoniazid to tween® albumin medium also without isoniazid and grown

(9) Am R Tubc 69 464 468 M h 1954

and 130 with streptomycin plus isoniazid Treatment was determined by random allocation and the clinical condition of patients in the three series was comparable Standard dosages were 100 mg isoniazid twice a day 1 Gm streptomycin daily and 5 Gm PAS four times a day For those who continued after three months of treatment the dosage of streptomycin was usually reduced to 1 Gm two or three times a week

Bacillary resistance to isoniazid was found in 64% of culture positive patients on isoniazid alone at three months and in 93% (28 of 30) at six months These 28 resistant strains represent 58% of the total patients for whom cultures were done For patients on streptomycin plus isoniazid 11% of the positive cultures were resistant at three months and 50% (two of four) at six months These two resistant strains were obtained from a total of 58 patients for whom cultures were undertaken (3%) In a three month period after treatment with isoniazid was stopped there was no evidence of any general reversion of isoniazid resistant strains either to a lower level of resistance or to sensitivity

For six months streptomycin plus isoniazid was as effective as streptomycin plus PAS in preventing emergence of strains resistant to streptomycin On streptomycin plus isoniazid 8% of the positive cultures were streptomycin resistant at three months and 0% (none of four) at six months on streptomycin plus PAS the corresponding figures were 6% and 29% (two of seven) Patients with initially PAS resistant organisms were not protected from the risk of developing streptomycin resistance by treatment with streptomycin plus PAS

Clinical Significance of Emergence of Drug Resistant Organisms during Therapy of Chronic Pulmonary Tuberculosis with Hydrazides of Isonicotinic Acid E O Coates Jr G M Meade William Steenken Jr E Wolinsky and G L Brinkman[8] (Trudeau N Y) report the clinical course of 43 patients (27 treated with isoniazid and 16 with iproniazid) with particular attention to emergence of drug resistant tubercle bacilli The patients represented a selected group of predominantly far advanced cases of chronic cavitary tuberculosis

Emergence of increased bacterial resistance to isoniazid or iproniazid appeared as early as the 4th week of therapy

(8) N w E gl d J Med 248 1081 1097 J 25 1953

density had developed each strain was inoculated subcutaneously into the groin of a guinea pig (Fig 43) All animals had progressive tuberculosis and bacilli isolated from these animals with one exception were susceptible to 0 2 μg isoniazid/ml

The evidence presented suggests that the cultures in the second experiment were composed of mixed populations of isoniazid susceptible and resistant bacilli This concept would perhaps explain the discrepancies in the literature concerning the virulence of isoniazid resistant tubercle bacilli for the guinea pig The entire bacterial population must be resistant to the drug or the loss of virulence for the guinea pig of isoniazid resistant strains will be obscured

In two experiments in mice the first group with inoculums of 0 2 mg of bacilli and the second of 0 5 mg there were no differences observed in the mice inoculated with isoniazid susceptible or resistant bacilli

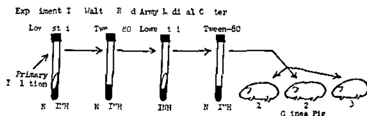
[Tubercle bacilli made resistant to isoniazid have been reported to have lost virulence for guinea pigs The present study suggests that this loss of virulence for guinea pigs may be a more constant phenomenon than the conflicting literature indicates Whether there is a clinical counterpart to this phenomenon with respect to changes of virulence for man is entirely unknown and would be hazardous to assume since there is no loss of virulence for another animal species the mouse —Ed]

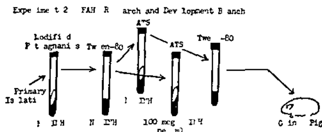
Pyrazinamide Isoniazid in Tuberculosis Walsh McDermott Louise Ormond Carl Muschenheim Kurt Deuschle Robert M McCune Jr and Ralph Tompsett[1] (New York Hosp Cornell Med Center) found that the antimicrobial action of pyrazinamide isoniazid in animals was superior to that of any of the standard antituberculous drugs administered either singly or together The effects produced were much more eradicative than those produced by other drugs and conceivably may have represented complete sterilization of the spleens of the infected animals

Treatment of 55 patients with pulmonary tuberculosis with pyrazinamide isoniazid for three months or longer and isoniazid alone thereafter resulted in sustained reversal of infectiousness in 90% substantial roentgen improvement in 75% and closure of all cavities in 65% of those with cavitary lesion Total daily dosage of pyrazinamide was 50 mg/kg body weight and of isoniazid 5 mg/kg Both drugs were given orally in equally divided doses twice daily Results

(1) Am R T b c. 69 319 333 M h 1954

to a suitable density Transfers were made from the tween® medium to Lowenstein medium containing known concentrations of isoniazid after suitable growth of the selected isoniazid resistant variants had developed transfers were again made to tween® albumin medium without isoniazid The isoniazid resistant strains were inoculated subcutaneously in the groin of guinea pigs Tubercle bacilli resistant to 25 and 50 μg isoniazid/ml did not cause disease in the guinea pig





Fg 43—E p m t l t h d n t dy ng v l e gu e p g of n d ta t t b l b ll (C t y f Mo s W C *et al* Am Re Tub c 69 464 468 M r h 1954)

Strains resistant to as little as 0 2 μg isoniazid/ml were attenuated in virulence

In the second experiment acid fast strains culturally consistent with Myco tuberculosis and resistant to 100 μg isoniazid/ml were transferred to modified Petragnani egg medium and after suitable growth transferred to tween® albumin medium containing no isoniazid After a reasonable density had developed transfers were made to one tube of American Trudeau Society medium without isoniazid and to another tube containing isoniazid 100 μg/ml Subculture from the ATS medium *containing no isoniazid was made to tween®* albumin medium containing no isoniazid and after suitable

of the hormone administration (3) The rebound exacerbations are frequently self limiting and are infrequently accompanied by extension of the disease (4) Exacerbations following administration of cortisone or corticotropin in short courses may be controll d by streptomycin (and presumably other antimicrobial agents) provided the infection is not drug resistant from previous therapy but such exacerbations may not be controllable by re umption of hormone administration Finally (5) patients with unsuspected or apparently arrested tuberculous disease who have been treated for other conditions with cortisone or with corti cotropin but the latter less frequently have been observed precipitously to develop acute forms of tuberculosis

The three clinical papers in this group report the simultaneous ad ministration of cortisone or corticotropin and antimicrobial agents to patients with tuberculous di ease In one instance corticotropin was used to overcome hypersensitivity reactions to antimicrobial drugs This ap pears to have been accomplished without deleteriou effect on the tuber culosis which responded well to the combined treatment and continued to respond well to the antimicrobial therapy after withdrawal of the corticotropin This indicates that the rebound phenomenon observed after corticotropin is prevented by simultaneous antimicrobial therapy

In the other two studies cortisone or corticotropin was administered together with antimicrobial therapy in attempts to prevent or relieve subarachnoid block and other complications of tuberculous meningitis It is perhaps too early to assess the extent to which these objectives may have been accomplished or to conclude whether the hormone therapy if used at all should be used routinely or only for special indications The rationale however appears to be good and the results indicate at least that corticotropin and even cortisone may be given in tuberculosis without harmful results when they are covered by anti microbial therapy

On the basis of the experimental results whenever corticotropin or corti one may be indicated in the presence of active tuberculosis the preferred drug would appear to be corticotropin However from both the experimental and the clin cal results the potentially harmful effects of cortisone can apparently be adequately covered by antimicrobial therapy This raises the furth r question now that an easily administered and usually well tolerated antituberculous agent is ava lable in the form of isoniazid whether this drug should not always be given to cover cortisone when this is administered systemically and cont nuously in the treatment of other conditions such as sarcoidosis lupus erythematosus and arthritis —Ed]

Effect of Cortisone and Streptomycin on Fxperimentally Induced Pulmonary Tuberculosis in Rabbits Thomas E Morgan Sidney H Wanzer and David T Smith[2] (Duke Univ) sensitized and partially immunized 52 white rabbits by subcutaneous injection of the relatively avirulent R_1v strain of Mycobacterium tuberculosis 22 other white rabbits were not s nsitized All rabbits were given an intratracheal injection of 5 mg of the Ravenel strain of bovine tubercle bacilli The disease was much more extensive and destructive

(2) J B t 67 257 263 M h 1954

were attained within the first six months of therapy (except for later cavity closure in two patients) No patient showed progression of disease on roentgen study In about half the group results had remained unchanged after nine months of observation

Three patients not included in the 55 died 2 of tuberculosis within the first 11 days of therapy and 1 of drug induced hepatitis on the 55th day of therapy Nonfatal hepatitis was also observed in five patients

It is concluded that pyrazinamide isoniazid exerts antituberculous activity in vivo of a sort superior to that of the other antituberculous drugs currently used either singly or together However the high incidence of hepatitis during therapy makes use of this regimen in present dosage inadvisable for treatment of tuberculosis

[Despite some discouragement consequent to the several severe toxic reactions here reported this development in therapy merits further study If it can be made more safe by reduction of pyrazinamide dosage, without important sacrifices in effectiveness it may become the optimal chemotherapy in tuberculosis because it appears to be the most powerful among known antimicrobial agents or combinations of agents against this infection Favorable therapeutic results are also reported by Campagna Calix and Hauser (Am Rev Tuberc. 69 334 1954) —Ed.]

↓ The following five papers are concerned with possible uses of the steroid hormones cortisone and corticotropin in combination with antimicrobial agents in tuberculosis Inasmuch as there have been warnings about the deleterious effects of these hormones on tuberculosis which have been widely interpreted as a proscription of their use in any circumstances in the presence of this disease an introductory comment is in order

Contrary to a widely held belief cortisone and corticotropin do not have identical effects on the course of tuberculous infection in experimental animals The first two of the following papers carries further the experiments of Bacos and Smith (1953 54 YEAR BOOK pp 181 184) and both confirm and extend Smith s own observations and those of others The principal facts which are now established experimentally are (1) cortisone even in moderate doses exerts an enhancing effect on the disease process (2) the deleterious effect may be completely controlled by simultaneous treatment with streptomycin unless the cortisone dosage is several times the human level (3) corticotropin has no deleterious effect in dosage equivalent to the human dose but does have a harmful eff ct in large enough do es (4) the harmful effects of even massive doses of corticotropin are neutralized by therapeutic doses of streptomycin

The hitherto established clinical evidence concerning the effects of the steriod hormones in human tuberculosis consists essentially of the following (1) Patient with active tuberculous disease to whom either corti one or corticotropin is administered in cu tomary therapeutic doses usually experience prompt symptomatic remissions frequently accompanied by regression of inflammatory manifestations (2) Such remissions are followed by rebound exacerbations of symptoms on cessation

In order to see that the dosage level of the two hormones was not responsible for this difference use was made of the lymphocyte depressing ability of the hormones to determine the relative physiologic amounts of each that were being ad ministered to the rabbits It was found that relatively more corticotropin than cortisone was being given so dosage can not account for the poor results obtained with cortisone

Cortisone exerts its deleterious effect both at and above human dosage levels whereas corticotropin could be admin istered in excess of human dose levels without harmful effect and was deleterious only at levels 20 times the human dose

Combined Corticotropin Therapy and Chemotherapy in Pulmonary Tuberculosis With Special Reference to Hyper sensitive Reactions L E Houghton[4] gave corticotropin in combination with streptomycin and para aminosalicylic acid (PAS) to 21 patients aged 12 60 with active pulmonary tuberculosis Eight had acquired hypersensitivity to strepto mycin or PAS or both Corticotropin suppressed all allergic reactions during chemotherapy On withdrawal of corticotro pin six of the eight had lost their hypersensitivity Very small doses of corticotropin suppressed gastrointestinal intolerance to PAS in five patients Three with alarming hypersensitive reactions had immediate benefit from corticotropin Five pa tients who were not hypersensitive were given the combined medication

The usual daily dose of corticotropin was 80 mg for four days 60 mg for three days 40 mg for three weeks 20 mg for two weeks then 10 mg for a week or longer

No adverse clinical or roentgen effects were seen either during or after corticotropin therapy for periods up to two years In some cases there was considerable even vital im provement during and after treatment Long standing lesions remained substantially unchanged radiographically but re versible lesions showed improvement and recent infiltrations were cleared effectively Clinical and roentgen improvement was noted in patients who had not previously responded well to streptomycin and PAS alone In many improvement was maintained after withdrawal of corticotropin

Most patients showed immediate and pronounced clinical improvement including decrease in temperature diminished

(4) La et 1 595 597 M r 20 1954

in the unsensitized rabbits Unsensitized animals given streptomycin had less disease than the other unsensitized rabbits Progressive disease of more severe nature than in controls developed in both sensitive and nonsensitive rabbits given 2 mg cortisone/day those receiving 20 mg daily died spontaneously with extensive fulminating disease Both sensitized and nonsensitized animals given streptomycin and 2 mg cortisone showed healing comparable to that seen in animals given streptomycin alone Animals receiving streptomycin and 20 mg cortisone had a diffuse disease similar in extent and severity to that in the control animals

These results support previous observations on the effect of cortisone on experimental tuberculosis in that cortisone alone exerts an enhancing effect on the disease process However if a small dose of cortisone up to twice the human dose is used with streptomycin the deleterious effect may be so reduced that the healing process may proceed as well as in rabbits receiving streptomycin alone With large doses of cortisone which exceed twice the human levels the disease is enhanced despite the action of streptomycin

Effect of Corticotropin (ACTH) and Streptomycin on Experimentally Induced Pulmonary Tuberculosis in Rabbits Sidney H Wanzer Thomas E Morgan and David T Smith[3] (Duke Univ) sensitized and partially immunized 52 white rabbits by the subcutaneous injection of the relatively avirulent R_1V strain of Mycobacterium tuberculosis 23 others were not sensitized All rabbits were later given 5 mg of the Ravenel strain of bovine tubercle bacillus intratracheally and all were treated with streptomycin corticotropin and a combination of the two All nonsensitized rabbits including controls showed much more extensive disease than the corresponding groups of sensitized animals

Corticotropin in a 10 unit/day dose had no damaging influence on the course of untreated tuberculosis nor did it interfere with the beneficial healing effect of streptomycin With a 20 unit/day dose the disease was slightly to moderately worse than that in controls However this dose did not interfere with the healing effect of streptomycin In a previous study [preceding article —Ed] both 2 and 20 mg cortisone/day made the tuberculosis worse

(3) J B ct 67 264 0 M h 1954

tempt to prevent formation of the thick basal exudate and to control development of tuberculous endarteritis Winifred C M Bulkeley[6] tried corticotropin intramuscularly or subcutaneously and isoniazid orally Isoniazid enters the cerebrospinal fluid in high concentrations and it was hoped that by controlling the cellular reaction with corticotropin the tubercle bacilli would be left free for antibiotic attack In 1950 for 10 cases of tuberculous meningitis the over all mortality rate was 60% this was reduced to 10% among 21 cases in 1951 when diagnosis was made earlier and streptomycin was given daily intrathecally The rate of 6 45% for the present series of 31 cases includes 8 who had had or continued to receive streptomycin intrathecally

In the present series the following regime was established (1) Six to 50 I U corticotropin was given at six hour intervals intramuscularly or 12 50 I U of the gel twice daily subcutaneously for one week if there was steady progress otherwise longer A patient hospitalized in coma usually could answer questions and help in feeding by one week (2) The first two doses of isoniazid by mouth were 8 mg /lb /day and thereafter 4 mg /lb (3) Streptomycin 0 02 Gm /lb /day not exceeding 1 Gm was continued until the temperature settled and improvement was assured then every three days (4) Para aminosalicylic acid 0 1 to 0 15 Gm /lb was given daily by mouth (5) Cerebrospinal fluid was examined biweekly for two to three weeks then weekly

Of the 31 earlier patients given streptomycin intrathecally 13 died whereas of the 31 treated by the new regime only 6 died There was no deafness or evidence of spread in the lungs while corticotropin was given Because most of the patients are small the avoidance of the ordeal and danger of the daily lumbar puncture is a great advance in management

[The improved results with this regimen as compared with earlier results with streptomycin by no means should be attributed entirely or necessarily even in part to the corticotropin Isoniazid is established as superior to streptomycin in the treatment of tuberculous meningitis It has without the addition of corticotropin obviated to a large extent if not completely the need for intrathecal treatment The dose of isoniazid here recommended (4 mg /lb /day = 8 8 mg /kg /day) is approximately the same as recommended in the United States (9 10 mg /kg day) during only the initial one to three weeks of therapy after which it is usually reduced to the 5 mg /kg level because of the risk of peripheral neuritis (see article by Lubing p 185) This toxic effect

(6) Brit M J 2 1127 1129 N 21 19 3

cough and sputum return of appetite disappearance of toxemia increase in weight and euphoria Relapse was not observed in any patient after withdrawal of corticotropin

Tuberculous Meningitis Combined Therapy with Cortisone and Antimicrobial Agents S J Shane and Clifford Riley[5] (Sydney Nova Scotia) report the recovery of five of seven patients treated with combined cortisone and antimicrobial agents As a rule treatment was begun with 200 300 mg cortisone daily orally when practicable but intramuscularly when oral administration was impossible This was usually accompanied by intramuscular administration of 1 Gm streptomycin or dihydrostreptomycin daily and PAS orally to tolerance In one case however streptomycin was withheld because of a history of severe hypersensitivity and was replaced by full doses of isoniazid in another all three antimicrobial agents were used No intrathecal streptomycin therapy was used in this series except in one case in which injections were given for a short period Cortisone therapy was maintained until there was decided improvement in the clinical and laboratory findings then gradually tapered off Antimicrobial therapy with one or more drugs was carried on for three to six months after cortisone had been discontinued

In one case the resolution of an established subarachnoid block occurred during treatment and in another there was evidence that development of an incipient block was suppressed by cortisone In one case clinical and bacteriologic relapse which had followed neurosurgical treatment (burr holes) was reversed by the combined therapy

Autopsy in the two fatal cases revealed a striking lack of cellularity in the tissues and exudates as compared with sections from patients treated by the conventional method This supports the theory previously suggested that the benefits which might accrue from cortisone therapy in this disease would be based on the known ability of the steriod to suppress the inflammatory process or bring about a reversal The use of cortisone in the presence of active tuberculosis appears to be safe provided it is adequately covered by effective antimicrobial therapy

Tuberculous Meningitis Treated with ACTH and Isoniazid Comparison with Intrathecal Streptomycin. In an at

(5) New E gland J M d 249 829 834 N 19 195;

(V.A Hosp New Orleans) this syndrome comprises an acute or chronic pulmonary disease of unknown origin characterized clinically by cough dyspnea and cyanosis and a progressive essentially afebrile course radiographically



Fg 45—R p t t m crosc p ect on f l g m p ti t F gu 44 n t p oneu d ll filt t on fib obl t p l f t nd m t pl f al l l g h g th f lm t mpl f H mm R h y d m (Cou t y f P body J W J t al A M A A h I t Med 9 306 8 4 D mb 1953)

by parenchymal and hilar densities with one definite characteristic—the tendency to eventual diffuse bilateral involvement pathologically by extensive fibrosis and round and plasma cell infiltrations within pulmonary interstitial tissue The disease does not respond to any form of therapy Three deaths followed cortisone withdrawal or slight reduction of

may be easily overlooked in the patient severely ill with meningitis and the resulting pain weakness in the extremities and bedsores be attributed to the disease —Ed]

MISCELI ANEOUS

Hamman Rich Syndrome [Diffuse Interstitial Pulmonary Fibrosis] Analysis of Current Concepts and Report of Three Precipitous Deaths Following Cortisone and Cortico tropin (ACTH) Withdrawal According to J Winthrop Pea body Jr Howard A Buechner and Augustus E Anderson[7]

F g 44 —P te o t w f l g n te b lat l d ff se fi ly od l r d t s th gb t R m k bl cl g f ll w d t t p th py t fter w thd aw l f t d t ot p n t oe tg n h g r d w th te d cy t w rd onfl y (C rte y f P b d J W J t I A M A A h I t Med 9 806 8 4 D b 1953)

(7) A M A A ch I t M d 9 806 8 4 De mb r 1953

Therapy of Sarcoidosis is discussed by Francis J Lovelock and Daniel J Stone[8] (New York City) Thirty nine patients with proved sarcoidosis showing involvement of the lungs or mediastinal and bronchopulmonary nodes were observed for several months to 3½ years Eleven were treated with cortisone (100 mg intramuscularly daily after an initially higher dose) and one with corticotropin (25 mg intravenously daily) 27 received no chemotherapy The duration of hormone therapy was 30 135 days (average about 60 days)

Most patients showed some roentgen evidence of improvement after hormone therapy but no criteria were found permitting prediction of the extent of such improvement A higher percentage of clearing was noted in patients receiving cortisone or corticotropin (64%) than in the patients not treated (44%) Roentgen evidence of clearing was not always maintained however as indicated by one patient who had rapid recurrence after each of two courses of cortisone therapy

The percentage of cases in which tuberculosis developed after therapy with cortisone and corticotropin did not differ significantly from that found in the untreated patients Rapid development of tuberculosis immediately following therapy in three patients however implies a serious hazard in this type of treatment This complication was noted only in Negroes

It is concluded that indications for the treatment of pulmonary sarcoidosis with cortisone or corticotropin are not yet established

Pulmonary Manifestations of Scleroderma Scleroderma of the lungs may clinically precede the development of cutaneous sclerosis and should be considered in the differential diagnosis of obscure causes of pulmonary fibrosis Wade H Shuford William B Seaman and Alfred Goldman[9] (Washington Univ) report five cases There was a striking similarity in roentgen appearance consisting of a widespread linear reticulated infiltration most marked in the lower half of the lung fields Conditions that cause the greatest difficulty in differential diagnosis of diffuse pulmonary lesions are sarcoid lymphangitic carcinomatosis of the lung pulmonary congestion and pulmonary fibrosis due to other causes Pulmonary

(8) Am J M d 15 477 483 O t b 1953
(9) A M.A A h I t M d 9 85 97 J ly 1953

corticotropin dosage The basic disease whatever its cause may have been suppressed during cortisone therapy becoming explosive however on liberation from exogenous and possibly endogenous adrenocortical control Cortisone or corticotropin therapy for any but the most desperately ill patients with diffuse indeterminate pulmonary fibrosis is not advisable Should these agents be used a permanent maintenance dose is advocated and should withdrawal be contemplated the utmost caution must be exercised

In man 31 cough progressive dyspnea fever and chest pain had for three month been unaffected by antibiotics Tachycardia slight cyanosis and hyperglobulinemia were noted Hemolytic Staphylococcus aureus was repeatedly isolated from the sputum Chest x ray revealed bilateral diffuse finely nodular mottled densities apparently following the pulmonary vascular pattern and fanning outward from the hilar areas throughout most of both lungs (Fig 44) Penicillin oxytetracycline chloramphenicol and erythromycin were ineffective After several days of treatment with 15 units of corticotropin by intravenous drip given over an eight hour period considerable subjective improvement was noted and the dose was reduced to 10 units daily In chest films taken 5 and 13 days after the institution of therapy only a fine reticular pattern was noted Symptoms nearly disappeared with cortisone therapy initiated with 100 mg /day orally and withdrawn gradually within a month For seven days before and four days after complete withdrawal of cortisone corticotropin in small doses was briefly reinstituted

Suddenly five days after corticotropin and nine days after cortisone were withdrawn extreme dyspnea and cyanosis reappeared and chest x ray disclosed a picture identical to the one seen initially Massive corticotropin and cortisone therapy failed to prevent development of fulminant respiratory insufficiency leading to death within 24 hours At autopsy all lobes of the lung were involved with pronounced round cell infiltration fibroblastic proliferation and metaplasia of the alveolar lining—characteristics of fulminating Hamman Rich syndrome (Fig 45)

[Although it was nine years after Hamman and Rich reported their first several cases in 1935 before they found another and although the three cases here reported, with several others publi hed even more recently bring the total of well authenticated cases up to only 25 this disease is not so rare as the literature would indicate It is being more frequently recognized particularly in the last year or two In only a very f w cases has the diagnosi been established ante mortem by lung biopsy which is the only means by which it can be made with certainty The precipitous deaths following withdrawal of cortisone or corticotropin which are here recorded are especially disturbing since these are the only agents yet tried which provide even an indication of possible benefit —Ed.]

Autopsy revealed diffuse interstitial fibrosis and terminal bronchiolar (so-called alveolar cell) carcinoma not suspected clinically in each Such an association has not been reported previously Metastases to distant organs were present in two cases

The pulmonary changes in scleroderma have been classified into cystic sclerosis and a compact sclerosis depending on the presence of actual dissolution of fibrotic lung tissue Shortness of breath is a common manifestation of pulmonary scleroderma A nonproductive cough is present early but later the cough is productive of purulent material Hemoptysis is unusual in contrast to its frequent occurrence in ordinary bronchiectasis Chest pain is uncommon A chest roentgenogram may reveal diffuse linear densities extending from the heart border to the lung periphery The lower portions of the lungs are predominantly involved Occasionally there is basilar mottling Honey combing is thought to be particularly suggestive of scleroderma The pleura is thickened and the sulci may be obliterated Disseminated pulmonary calcifications may occur in patients with associated calcinosis An area of pulmonary consolidation with subsequent resolution to a cystlike lesion has been observed The bronchovascular markings are increased and the hilar area may be widened

Pulmonary symptoms in patients with scleroderma were previously thought to be related to involvement of the chest wall with consequent limitation of expansion and susceptibility to infection However with the demonstration of pulmonary scleroderma and alveolar fibrosis a more important mechanism would appear to be that of impairment of gaseous diffusion Cardiovascular lesions should be sought in such circumstances as they are probably as common as pulmonary ones In fact some workers feel that pulmonary fibrosis is secondary to changes in the pulmonary vasculature

Roentgenographic Aspects of Complete and Incomplete Pulmonary Infarction are discussed by Marcus J Smith[2] (Santa Fe N M Clinic) The complete infarct produces an abnormal density variable in shape Depending on its location it may be pyramidal or triangular round oval or irregular Odd and round shadows may be caused by superimposition of multiple infarcts and should be dissected by multiple films

(2) D Chest 23 532 546 May 1953

sarcoidosis is usually associated with bilateral hilar adenopathy which is rare in scleroderma although one patient did have prominent hilar shadows suggesting lymph node enlargement None had significant emphysema as determined by roentgen criteria In scleroderma roentgen changes in teeth bones soft tissue calcification and esophageal changes may help in the diagnosis

Acute pulmonary edema (azotemic edema) consisting of bilateral homogeneous central areas of increased density with sparing of the apexes bases and periphery occurs with varying frequency in the collagen diseases However this type of pulmonary reaction may represent a complication of the disease and does not reflect the primary pathologic process It is not generally recognized that renal failure may be the cause of death in scleroderma The pulmonary manifestations of disseminated lupus erythematosus usually consist only of pleural effusion parenchymal involvement is rare and when it does occur tends to resemble atypical pulmonary edema Pulmonary manifestations in polyarteritis nodosa occurring in 25% vary depending on whether the lesions are acute or chronic gross or microscopic isolated or confluent The only characteristic x ray feature is constant change which contrasts with the constancy of the manifestations in scleroderma Pulmonary edema may also occur as in scleroderma this may represent a complication superimposed on the underlying basic pathologic alterations Hilar enlargement is common in polyarteritis nodosa with pulmonary involvement but is unusual in scleroderma

Pulmonary involvement is unusual in rheumatoid arthritis although several instances have been described with diffuse mottling resembling miliary tuberculosis that tends to resolve completely Rheumatic pneumonia differs greatly from scleroderma clinically Roentgenograms usually show vascular congestion or pulmonary edema and do not resemble those of scleroderma

Pulmonary Fibrosis and Terminal Bronchiolar ("Alveolar Cell) Carcinoma in Scleroderma Jacob Zatuchni William N Campbell and Chris J D Zarafonetis[1] (Temple Univ) report three cases of scleroderma with symptoms simulating bronchiectasis tuberculosis and pneumonitis respectively

(1) C 6 1147 1158 Nov mb 1953

wall destruction and heals by resolution in two to four days In three cases faint sharp short (2-4 cm) lines were seen in chest films coincident with the clinical occurrence of pulmonary emboli (Fig 47) These were situated transversely or obliquely and were preceded by negative roentgenograms they changed character in two to seven days These shadows differed from those representing platelike atelectasis because the latter are long and horizontal occur at the bases of the lungs and are associated with elevation of the diaphragm or intra abdominal lesions Pulmonary scars could be ruled out

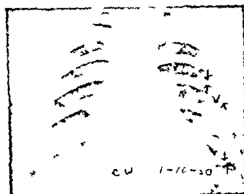


Fig 47—M n 28 L ea hadow bel ev d to repr sent n omplet nfa cts in l w two-th d of l ft l g ry) g n po t on e a ix day n e l These corre po ded w th l l iden f pulmonary mb l Th w mplet lea g n 10 days (Cou t y of Sm th M J D Ch t 23 53 546 May 1953)

since previous films were negative The position of the shadows differed from that of the lung fissures ruling out interlobar pleuritis

Embolism without infarction (or probably with incomplete infarction) occurs frequently a sharp area of pulmonary ischemia (increa ed radiolucence) may be a roentgen sign of the situation as described by Westermark and others Clinical evidence of a pulmonary embolus associated with negative roentgen evidence may also warrant this diagnosis

Pulmonary Paragonimiasis Review with Case Reports from Korea and the Philippines is presented by Francisco T Roque Russell W Ludwick and J Carroll Bell[3] (Fitzsimons

(3) A n I t Med 38 1206-1221 J 1953

including spot films The borders are sharp if seen in the obliquity in which its greatest thickness is penetrated The infarct is always in contact with one or more pleural surfaces the cardiac margin is rounded or hump shaped The long diameter is always parallel to the largest pleural surface involved The occasional odd shapes may suggest the diagnosis (Fig 46) The location is variable but there is some predilection for the right lower lobe On healing a scar consisting of masses of dense tangled elastic fibrils which may be visible on



Fg 46—M 60 h d nd h ply d fi d h m g ou m n t or gment f ght pp l b P p t d g w p ph l c om of l ng Le n wa x d nd f d t be h ra t t pulm y nt t (Co rt sy f Sm th M J D s Ch t 1 53 546 M y 1953)

the film as an irregular linear band is usually left but the infarct may clear completely

Many secondary signs of pulmonary emboli have been described (1) clouding in the region of the costophrenic angle (2) accentuation of the hilar vessels on the side of the lesion (3) prominent pulmonary conus (4) elevation of the diaphragm on the affected side and (5) pleural effusion These secondary signs are misleading except for the small pleural effusion in the presence of contiguous parenchymal disease in a noncardiac patient in this situation it may be valuable indirect evidence of an infarct

The incomplete infarct begins with edema and fluid and blood cells in the alveoli this does not progress to alveolar

1932 discusses the pathogenesis of the eosinophil reaction Many authors believe the eosinophil reaction in Loffler s syndrome is an allergic phenomenon However this presupposes a previous sensitization Generally there is an 8 10 day interval between exposure to the allergen and sensitization It is therefore improbable that an eosinophil reaction that appears in a shorter time is of allergic origin

Experiments with guinea pigs showed that within two days after primary infestation with ascaris larvae an eosinophil infiltrate appeared in the mucosa of the gut In a self infestation experiment Essellier and Koszewski noted the first appearance of lung infiltrates within six days Massive infiltrates appeared within eight days Clinically medicated oil injected daily into a patient resulted in the appearance of a fleeting lung infiltrate and eosinophilia in the blood within five days In animal experiments eosinophil infiltration of the lungs was seen within 10 hours after the first intravenous administration of oil

Blood eosinophilia in allergic reactions rises steeply and reaches its maximum in three to four days From the literature it is noted that human volunteers infected with ascaris larvae showed slow progressive increase in the number of blood eosinophils in the first 10 days Similar conditions occurred in the guinea pig

By definition the allergic organism reacts differently on re exposure to a noxious agent to which it has been sensitized In experimentally induced Loffler s syndrome there were no temporal deviations with respect to eosinophil infiltrate or blood eosinophilia A second infestation with ascaris larvae in the guinea pig results in the same eosinophil reaction as the first time The same reaction occurs in Loffler s syndrome after oil injections However in other cases induced by different noxious agents the possibility of an allergic origin of Loffler s syndrome is not excluded

Etiology and Management of Spontaneous Pneumothorax are discussed by Richard L Rapport Alfred A Thurlow Jr and Karl P Klassen[5] on the basis of 36 cases The etiology is obscure in most instances (64% in this series) and the condition must be labeled idiopathic In many if not all of these cases it is due to rupture of subpleural blebs or bullae which

(5) A M A A h S g 67 66 275 A g t 1953

Army Hosp Denver) Paragonimiasis is usually contracted in man by ingestion of raw or poorly cooked fresh water crustacea such as crabs and crayfish It is doubtful whether the crustacean carrier is an absolute biologic necessity and the authors experience indicated that the disease may be contracted by ingestion of contaminated drinking water

Symptoms and physical findings depend on the stage the disease has reached After invasion of the lung parenchyma is complete hemoptysis presence of opercular eggs in the sputum and evidence in the chest roentgenogram are characteristic Shortness of breath fever malaise fatigability and anorexia may be present in patients with extensive pulmonary involvement There is no chronic cough but the patient coughs in a conscious effort to expel material from the lungs Uncomplicated pulmonary paragonimiasis rarely causes significant systemic symptoms and patients most often appear surprisingly healthy Some Oriental patients never seek medical aid even though they have hemoptysis and the diagnosis is made only incidentally during investigation of some unrelated complaint Secondary anemia does not usually develop even after many years of periodic blood spitting One of the most characteristic features is the history of intermittent hemoptysis in an otherwise asymptomatic patient who is well nourished afebrile and without any stigmas of chronic pulmonary disease

Eosinophilia is common in these patients but most often occurs in association with other helminths After successful antihelminthic therapy eosinophilia usually disappears Similarly the total white blood cell count is often normal or only slightly elevated in uncomplicated cases and the differential count is normal or discloses only slight granulocytosis No roentgen findings can be considered typical of pulmonary paragonimiasis The picture simulates pulmonary tuberculosis so closely that if a patient has been in an endemic area paragonimus infestation should be considered when chest films suggest tuberculosis but tubercle bacilli cannot be found

[The disease is most common in the Philippines Japan Korea and Formosa and should be particularly considered in differential diagnosis of patients who have been in these areas —Ed]

Fleeting Infiltrates of Lung with Eosinophilia of Blood W Loffler[4] (Zurich) who first described this syndrome in

(4) Act all gol (s pp 3) 6 186 193 1953

in spontaneous pneumothorax. If the principles here set forth are observed the results will be favorable and recovery rapid.—Ed.]

Mechanical Production of Expiratory Flow Rates Surpassing Capacity of Human Coughing Alvan L. Barach Gustav Beck and William Smith[6] (Columbia Univ) describe a mechanism by which negative pressure is applied to the upper respiratory passageway by a mask or mouthpiece at the moment the peak inspiratory pressure is reached The exsufflation with negative pressure (E.W.N.P.) device includes a blower to inflate the lungs gradually with the positive pressure desired i e. 20-35 mm. Hg and an additional blower which develops a negative pressure at 20-40 mm Hg with high volume flow rates the latter may be increased by a setting on a Variac to 15 L./second or more or twice the air velocity of the cough of most healthy individual A valving arrangement is connected by rubber tubing to the positive and negative pressure outlets of blower and mask The lungs are slowly inflated by air from the positive pressure blower and at the peak inspiratory pressure the patient (or attendant) pulls a trigger which opens the valve to the negative blower The inspiratory pressure may also be terminated after 2.5 seconds by a solenoid valve operated by a time-delay relay circuit The increased pressure gradient established between the pressure of the inflated lungs and the negative pressure maintained in the mask is responsible for air being expelled from the lungs at a flow rate greater than that previously obtained in maximal human coughing

Expiratory volume flow rates of 10 000 cc./second were produced by E W N P in normal individual and in patients with respiratory difficulties Average expiratory flow rate initiated by the portable apparatus used was 15% higher than that produced by a cough of maximal effort in 15 normal subjects and about double that of 20 patients with bronchial asthma pulmonary emphysema bronchiestasis or poliomyelitis Use of E W N P was generally of therapeutic value when retention of bronchial secretions was the cause of pulmonary atelectasis or impairment of respiratory function

Enzymatic Debridement Particular Reference to Trypsin and Desoxyribonuclease in Control of Cough and Sputum Associated with Tuberculosis Seymour M Farber R Daniel

(6) T A Am Phy n 66 315 J 4 1953

may be congenital or due to local structural changes produced by obstructive emphysema pneumonitis cystic bronchiectasis or tuberculosis Tuberculosis is an infrequent cause (6%) A history of indirect trauma preceding collapse is unusual Efforts should always be made to establish the responsible factor before the condition is considered idiopathic

If collapse is minimal (less than 25%) specific treatment is probably unnecessary The lungs of patients with such minimal collapse re expanded fully in a relatively short time (maximum three weeks) without surgery Thoracentesis proved ineffective Evacuation of air from the pleural cavity by this method fails to hold the ruptured bleb against parietal pleura long enough for healing to occur Moreover the needle may traumatize the expanding lung If collapse is greater than 25% active surgical *intervention is the treatment of choice* Insertion of a Pezzer catheter into the pleural cavity with water seal drainage is easily performed under local anesthesia *Patients treated by thoracotomy tube were allowed to return* to work immediately after hospital discharge For patients treated nonspecifically bed rest with gradual progressive ambulation for four to six weeks before return to work has been advised Thoracotomy and definitive surgery such as resection of blebs segments or lobes are indicated in progressive hemopneumothorax persistent bronchopleural fistula and multiple recurrences

The chief symptoms chest pain and dyspnea are usually relieved shortly after insertion of a thoracotomy tube Apprehensive patients whose symptoms persist despite a re expanding *lung may be safely given narcotics without fear of re*spiratory depression This is not true for patients with collapse

Evacuation of air by any means available *is absolutely* indicated for tension pneumothorax Use of oxygen is seldom indicated except in the presence of severe cyanosis Efforts should be directed to keeping the bronchial secretions thin and watery Since a bronchopleural fistula is present in all *instances* antibiotics should be given both systemically and by aerosol

[The trend is toward more frequent and earlier surgical intervention

The Blood *and* Blood-Forming Organs

WILLIAM B CASTLE M.D

Gorman David A Wood Orville F Grimes and Samuel L Pharr[7] (Univ of California) administered trypsin alone or with desoxyribonuclease by aerosol inhalation to 24 patients with pulmonary tuberculosis who had excessive cough and raised moderate to large amounts of sputum Initially an oral nebulizer was used but later a nasal nebulizer was substituted Trypsin doses ranged to 100 000 150 000 units daily for an average of 10 days to 11 patients 16 others also received desoxyribonuclease in doses ranging from 2 mg daily for 4 days to 5 mg daily for 11 days

Although trypsin alone had little effect with desoxyribonuclease it reduced cough and viscosity of sputum in most patients and made it easier to raise the sputum without decreasing its volume Results were not impressive however except in three patients whose cough substantially decreased

Significant side reactions were encountered in 71% Local irritating effects of trypsin and perhaps also of desoxyribonuclease included hoarseness aphonia severe cough and hemoptysis Fewer side reactions followed nasal than oral inhalation Generalized toxic reactions included severe dyspnea and *wheezing (usually immediately after inhalation)* chills and fever (four hours later) and generalized rash The incidence of these reactions was not affected by the method of enzyme administration Cytologic studies of the sputum of 16 patients disclosed increased metaplasia of cellular components in 12 specimens

It appears that trypsin and desoxyribonuclease should not be used routinely in treatment of tuberculous patients with productive cough The toxicity of the treatment outweighs its slight benefits

(7) J Th a S g 27 45 54 J y 1954

PART III

THE BLOOD AND BLOOD FORMING ORGANS

GLNERAL CONSIDERATIONS AND SPECIAL TECHNICS

Human Blood Group Chimera A unique example of a human being with red cells representing two different blood groups is reported by I Dunsford C C Bowley Ann M Hutchison Joan S Thompson Ruth Sanger and R R Race[1] (Lister Inst London)

Healthy woman 25 donated blood which appeared to contain a mixture of A and O red cell Anti A serum caused large agglutinates but 61% of the red cells were unagglutinated This appearance could ordinarily result only from a large transfusion of O blood into an A recipient However the patient had never had a transfusion and further samples confirmed the original findings

Because in cattle vascular anastomoses are usually present between twin embryos and as reported by Owen red cells belonging to one twin may take root in the other and continue throughout the life of the animal to produce red cells with genetically foreign antigens the patient s blood was studied from this point of view The O cells were shown to have differ ent subgroup genetic specificities from the A_1 cells The pa tient s own cells were judged to be group O because she secreted O (H) antigen in her saliva but not A antigen Her twin brother had died at the age of 3 months and the A cells of the patient s blood were presumably living descendants of his primordial blood

Alternative explanations such as somatic mutation and dispermia were considered highly improbable respectively because of the three separate genetic differences in the two types of red cells and because the patient displayed no obvious signs of bodily asymmetry The patient s normal physical and sexual development indicated no evidence of endocrine influ ence similar to that of the bovine twin or the freemartin

(1) B t M J 2 81 J ly 11 1953

respiration When oxygen tension rises normally at birth the hemoglobin and red cell levels drop but if anoxia persists the high blood levels are maintained [Presumably the parallel drop in hemoglobin and red cells in the normal postnatal infant which is exaggerated in the premature or twin baby indicates that the total marrow mass is insufficient for normal erythropoiesis without the additional stimulus of the anoxia encountered in utero —Ed]

The compensatory polycythemia of cyanotic congenital heart disease is a response to marrow anoxia but in some cases the hemoglobin values do not increase commensurately and relative anemia arises which has the pattern of iron deficiency anemia *with hypochromia and microcytosis* This is attended by anoxic symptoms The anemia responds well to iron and transfusions are helpful but there is danger of vascular thrombosis The therapeutic response to iron results in production of red cells of more normal size and hemoglobin content and the anoxia is relieved As the hematocrit approaches 80% the former anoxic symptoms recur At the same time blood viscosity is greatly increased and is probably responsible for the reappearance of symptoms In therapy it is desirable to avoid raising the hematocrit above 70% and since the rise continues after cessation of therapy it is perhaps advisable to discontinue iron therapy when the hematocrit reaches 60%

Bone Marrow Pressure in Leukemic and Nonleukemic Patients Nicholas L Petrakis[3] (Univ of California) points out that many patients with leukemia and multiple myeloma bleed through the marrow puncture needle at the time of aspiration although hemorrhagic tendencies may not be present clinically This fact and the not infrequent presence of throbbing pain and bone tenderness suggest that there may be some increase of pressure within the marrow cavity

The marrow pressures of 14 nonleukemic patients 10 with leukemia and 1 with myeloma were measured by a strain wire gauge attached to the marrow needle Respiratory rate and *amplitude and ECG tracings were recorded simultaneously* Pressures of sternal and iliac crest marrow cavities were determined simultaneously or serially The patients were at rest without sedation and except for those with leukemia or hem

(3) *J Cl I t 33 27 34 J y 1954*

Examination of the blood of 58 pairs of dissimilar and of 82 pairs of apparently identical twins disclosed no evidence of another individual with mixed blood groups

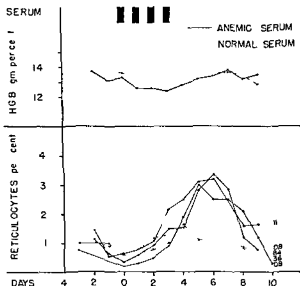
Hematologic Adjustments to Cyanotic Congenital Heart Disease are described by Abraham M Rudolph Alexander S Nadas and Wayne H Borges (Boston) In some patients with cyanotic congenital heart disease the polycythemia is attended by relatively low hemoglobin values Seven such patients with relative anemia' were given 150 mg ferrous sulfate daily and the response of the red cells hemoglobin and hematocrit observed regularly In some blood viscosity studies were also done A second group of eight newborns with congenital heart disease were similarly observed at two to four weeks intervals for three to nine months to follow the natural course of the blood values in this disease Their diets contained no supplementary iron

The first group had rapid general improvement with relief from anoxic symptoms and increase in weight in two to six months There was associated accentuation of the cyanosis Later gradual regression with return of the anoxic symptoms took place corresponding to an increase of the hematocrit above 70% To attempt to relate the recurrence of symptoms with the red cell mass viscosity studies were done These showed that at low hematocrit values a rise in hematocrit has little effect on blood viscosity but at high hematocrit levels minor hematocrit changes greatly increase blood viscosity the critical region being 75 80% This corresponds well with the clinical findings

Of the eight untreated infants three were not cyanotic and these developed the expected anemia of infancy Three others were mildly cyanotic and behaved similarly until the third month when polycythemia with relative anemia developed The two others with pronounced cyanosis did not have an anemia but maintained high red cell and hemoglobin levels for three or four months when divergence of these values occurred and relative anemia supervened This throws interesting light on the drop in hemoglobin and red cell count in the first two or three months of life in normal infants In the fetus in utero the oxygen tension in the blood is only 11 mm Hg compared to 40 mm after initiation of pulmonary

(2) Ped at cs 11 454 464 M y 19 3

been made to demonstrate this in the serums of anemic ani mals Although results have been rather inconclusive reticu locyte responses have been observed after injection of ane mic serum homologously into rabbits and rats A Erslev P H Lavietes and G van Wagenen[4] (Yale Univ) studied this problem in adult Macaca mulatta monkeys Three mon keys were made anemic by bleeding two or three times



F g 48—T p g h m gl b lu f m nk y g a m s rum d m k y g m l m B tt m d d l t l yt t Block d t f d y wh b m m l m w j ted o ly (Cou t y f E l A t l P oc Soc E p B l & M d 83 548 550 J ly 1953)

weekly and the anemic serum was pooled when the hemo globin levels fell below 7 Gm /100 cc Part was kept at 4 C *for two weeks the rest was frozen in a dry icebox* Serum from normal monkeys was similarly separated and stored Serum was given intravenously to four monkeys on each of four consecutive days the total amounts being 6 10% of the animals body weight Daily blood counts including platelet and reticulocyte counts were made on capillary blood

Serum from anemic monkeys injected into normal monkeys produced reticulocytosis up to three times the normal values

(4) P Soc E per B l & M d 83 548 550 J ly 1953

orrhagic tendencies were premedicated with 50 100 mg hepa rin to prevent clotting A variety of physiologic stimuli were applied during the tests

Marrow pressures in nonleukemic patients were uniformly low pressure in the sternum varying frequently with depth of respiration but the iliac crest marrow was not so affected Pressures in both sites rose with forced expiration and coughing with an initial slight decrease during the short inspiratory phase of the latter Pressure also varied with change of body position For example there was a progressive increase in iliac crest pressure when the patient moved from lying to sitting to standing erect to squatting Decrease in pressure followed the Muller maneuver (inspiratory effort with glottis closed) and injection of epinephrine Pulse wave analyses showed only simple pulsation with what was probably superimposed venous pulsation

In leukemic patients both marrow pressures were increased the increase being greatest in patients with acute leukemia The response to stimuli was similar to that in non leukemic patients but was exaggerated Pulse wave analyses showed dicrotic notching in patients with highest mean pressures and pulse pressures There was no correlation between mean and pulse pressures and the degree of anemia

The marrow behaves as a semiclosed cavity changes in pressure depending on intramedullary blood volume When venous return is obstructed the mean marrow pressure increases and pulse pressure decreases Constriction of the afferent arteries either mechanically or pharmacologically decreases both mean and pulse pressures Intramedullary pressure varies with physiologic activity and may like such postulated factors as growth pressure and cell maturity affect blood cell delivery from the marrow

Some patients with myeloma experience pain on coughing or straining It is possible that the sudden elevation of intramedullary pressure resulting from such effort distorts the a teries and arterioles bearing sensory nerves and thus produces pain It is also possible that long continued exaggerated arterial pulsations in the marrow may contribute to erosion of the trabeculae often seen in leukemic bone marrow

Erythropoietic Stimulation Induced by "Anemic" Serum The existence in the blood serum of a factor governing red cell production has long been suspected and attempts have

sinic hemolytic anemia described by Chaufard and Vincent (1909) Although the mechanism of hemoglobinuric bilious fever is as yet unknown a disease of autoaggression is suggested Apparently then several different processes may cause the body to produce antibodies injurious to its own red blood cells but the precipitating factor is still unidentified

Of the second type the antiplatelet autoantibodies thromboagglutinins and thrombolysins have been found only in the serums of patients with idiopathic thrombocytopenic purpura but all workers who have demonstrated them have concluded that just as there is acquired hemolytic anemia with autoantibodies so there is acquired thrombocytopenic purpura with autoantibodies

The third type comprises antileukocyte antibodies Nenna and the author have recently detected a powerful leukoagglutinin in the serums of 12 patients with leukopenia or agranulocytosis This discovery opens new horizons for the leukocyte series Certain cases of agranulocytosis may well constitute the third member of the triad of hematologic diseases with autoantibodies and continued investigation may uncover antileukocyte isoagglutinins Practically the presence of leukocytes in blood to be used for transfusions may be responsible for sensitization or may support an already acquired sensitization In such cases the transfusion of blood free from leukocytes or containing certain kinds of leukocytes might be indicated

Numerous observations suggest the presence in some patients of antibodies directed against two or even all three blood lines as for example reportedly coexistent thrombocytopenic purpura and hemolytic anemia The apparent conflict between the immunologic origin of these various phenomena and the classic concept that a body cannot be autoantigenic can be resolved by supposing that the various agents responsible for diseases in which the antibodies appear produce changes in cellular surface either directly (by viral fixation) or indirectly (by enzymatic action) The appearance of the antibodies would then be precipitated solely by antigens that had undergone modification thereby becoming foreign to the body According to this hypothesis diseases of autoaggression would result from the disordered mobilization of one of the body s own mechanisms of defense

but had no other effect on peripheral blood Injections of normal serum produced no changes whatever (Fig 48)

In the limited study undertaken it was impossible to assess the effect of freezing the anemic serum however its activity was not thereby destroyed Similarly the importance of age and dosage of the serum was not evaluated

Thus there can be demonstrated in the serum of anemic primates a humoral factor capable of stimulating red cell production in the normal animal when large quantities of the serum are used

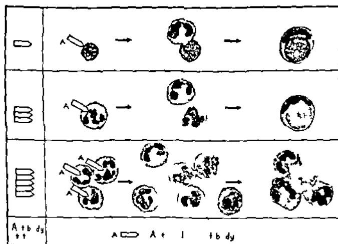
[These observations confirm the similar fundamental demonstration in rabbits reported by Erslev (1953 1954 YEAR BOOK p 231) —Ed]

Immunohematology and Diseases of Autoaggression J Dausset[5] (Paris) distinguishes antibodies capable of acting on the cells of the blood without the help of any other substance from those which can act only in the presence of some substance to which the body has become sensitized The first group comprises the antierythrocyte and antiplatelet and antileukocyte pan antibodies which give rise to various usually chronic forms of anemia purpura and agranulocytosis Apparently these are the only genuine auto or pan antibodies The second group comprises allergic antibodies directed against some foreign substance (fava bean sedormid® pyramidon®) which acts as an antigen In discussing the disease of autoaggression the author confines his attention to the first group

The first type antierythrocyte autoantibodies may be arbitrarily divided into two classes agglutinins and hemolysins The autoagglutinins are responsible for certain conditions now fairly well understood clinically and biologically whose essential mechanism is still obscure The commonest of these is acquired hemolytic anemia with warm antibodies (Hayem Widal type) occurring as a complication of malignant disease of the hemopoietic system (lupus erythematosus or periarthritis nodosa) in 30% in the other 70% it appears to be idiopathic Acquired hemolytic anemia with cold antibodies on the other hand differs in onset in that it usually appears as a complication of a viral infection like atypical pneumonia or grippe The autohemolysins are responsible for one well known and one still poorly defined type of disease syphilitic paroxystic hemoglobinuria a frigore and hemoly

(5) Schw med Wchnschr 83 1037 104 Oct 24 1953

Nucleophagocytosis and LE Phenomenon P Miescher[7] (Univ of Lausanne) advances the theory that an immunologic mechanism may be responsible for the nucleophagocytosis or the LE phenomenon His theory is based on (1) the fact that patients with disseminated lupus erythematosus sometimes have hematologic changes such as hemolytic anemia and thrombocytopenia which are probably immunologic in origin and (2) experimental production in vitro of changes



Fg 49—Hypoth f mm l g m ha m f LE ph e n (C t y f Me h P S hw m d W h h 83 104 1043 Oct 24 1953)

similar to those of the LE phenomenon These changes were produced by adding antispleen antithymus and antinuclear antiserums to plasma rich in leukocytes

Three stages shown in the diagram in Figure 49 can be distinguished in the changes produced by the immunologic process When the titer of antinuclear autoantibodies in patients presentin the LE phenomenon is low phagocytosis affects chiefly the bare lymphocytic nuclei those still protected by cytoplasm are not yet subject to attack and the resultin forms closely resemble tart cells Later in stage 2 if the titer of antinuclear *antibodies is high enough* intracellular nuclear changes typical of the LE phenomenon are

(7) S hw m d W h sch 83 1042 1043 Oct 24 1953

Simplified Method for LE Cell Test Results of Three Year Study of 700 Tests in Many Disease States Edmund L. Dubois[6] (Univ of Southern California) using a simple technic increased the diagnosis of systemic lupus erythematosus fourfold 72 new cases were discovered and 380 tests performed in these alone

TECHNIC —To 2 drops of an aqueous heparin solution (50 mg/cc) in a 15 cc tube add 10 cc venous blood or several cubic centimeters of bone marrow and shake well Set tube at room temperature for 30 60 minutes Centrifuge at about 2 000 rpm for five minutes or until the three layers separate With a Wintrobe pipet remove supernatant plasma then transfer 1 cc buffy coat to a Wintrobe tube Centrifuge again at 2 000 rpm for five minutes or until the layers separate then remove plasma Then aspirate the buffy coat and smear on three glass slides To make a thin part of the smear pull smearing slide to and fro over one half of the blood film Stain preparations with Wright s stain as usual Examine the film especially at the edges for at least 10 minutes If any abnormalities are found review the slide for longer time and make another preparation.

This technic is as accurate as more complex methods using animal marrow cantharides vesicles or clotted blood In interpretation of the LE preparation four abnormalities are looked for rouleaux formation hematoxylin bodies rosettes and LE cells Of these only the LE cells are diagnostic The others are suggestive and indicate that further tests should be made Both marrow and blood should be tested for frequently one alone may give a positive result It may be necessary to perform repeated tests over weeks to years to confirm the diagnosis

No false positive results were noted but negative results were obtained in 30% of typical clinical cases With adequate corticotropin or cortisone therapy LE cells disappear within four to six weeks but may reappear if dosage is interrupted or in difficult cases

The test should be performed on all patients with fever polyarthralgia pericarditis pleurisy ascites discoid and acute lupus like lesions bizarre skin lesions convulsions ocular hemorrhages and exudates nephrosis and nephritis persistent nausea vomiting abdominal pain diarrhea hepatosplenomegaly Raynaud s phenomenon depression of any element of peripheral blood hyperglobulinemia or false positive results of serologic tests for syphilis It is unusual to obtain a positive result in an afebrile untreated patient

(6) A M A A h I t. Med 9 168 184 A gu t 1953

rabbit and the buffy coat of its blood showed none of the phenomena described The buffy coat of the patient s blood likewise failed to reveal such changes

The ability of rabbit plasma to induce nucleophagocytosis appears to be a result of sensitization to leukocytes and the similarity of the changes observed to the LE phenomenon suggests that the latter may be due to a similar mechanism The occurrence of tart cells hitherto regarded as histiocytes and transitional stages between it and the LE cell suggest that these cells may be related The severe changes noted in the later preparations probably indicate a higher antibody titer or they may be due to different antibodies simultaneously evoked by this crude antigen

[Patient with extreme sensitivity to penicillin have been reported to show LE cells —Ed]

Secondary Hemochromatosis II Report of Case Not Attributable to Blood Transfusions is presented by Robert J Goldish and Arthur C Aufderheide[1] (Minneapolis)

Man 55 in 1930 was found to have hepatomegaly and moderate hypochromic anemia Chest and alimentary tract x rays showed no abnormalities He was given iron orally for two months and later liver injections at times with iron The complexion became muddy and the abdomen distended Subsequently abdominal distention increased and the skin darkened there were also a few anginal episodes In 1950 there were 3 020 000 red cells and hemoglobin content was 8 Gm Sulfobromophthalein retention was 14% in 45 minutes Transfusion and later iron and vitamin B_1 therapy had no effect A skin biopsy showed hemochromatosis and polyuria polydipsia and polyphagia appeared Dyspnea and weakness increased

In December 1951 there were severe dyspnea and dependent edema distended abdomen and palpable liver and spleen Blood studies showed 3 110 000 red cells hemoglobin 8 Gm and hematocrit 31% smears showed hypochromasia occasional normoblasts stippled red cells macrocytes target cells and Howell Jolly bodies 0 5% of the red cells contained siderotic granules there were 4% reticulocytes There was no sickling but slightly increased red cell fragility X ray studies showed left sided effusion and some cardiac enlargement but normal alimentary tract In two brothers and a nephew hematologic findings were normal In view of high fasting blood sugar values with glycosuria the patient was given a low sodium diabetic diet and insulin as required In addition he received folic acid and vitamin B_{12} but the anemia persisted Another skin biopsy showed iron pigment scattered throughout and liver biopsy revealed marked cirrhosis and large iron deposits Six months later he died in severe congestive failure with fibrillation and there was hyperglycemia

(1) Blood 8 837 844 S pt mb 1953

produced and the resulting nucleolytic material is phagocytosed by other polynuclear cells Rosettes consisting of fused nuclear masses from several leukocytes surrounded by other leukocytes are found when the antibody titer is very high (stage 3) The antithymus and antispleen serums produced changes characteristic of the first stage only probably because they contained anticytoplasmic antibodies and the resulting cytoplasmic antigen antibody reaction prevented more extensive nuclear injury Experiments with antinuclear serums obtained by sensitizing guinea pigs with nuclei isolated from human spleen cells and human lymphocytes however have produced changes corresponding to stages 2 and 3

Production of Nucleophagocytosis by Rabbit Antileukocytic Serum. The supposition that the LE phenomenon may be due to an antibody led Hyman J Zimmerman John R Walsh and Paul Heller[8] (V A Hosp Omaha) to attempt to reproduce the phenomenon by producing an antileukocytic serum

METHOD—The buffy coat layer of blood from a patient with myeloid leukemia was allowed to dry then finely ground One gram of this material was suspended in 100 ml isotonic saline and injected subcutaneously into a rabbit 0 5 ml being the initial dose then 1 ml every three days for eight weeks Plasma samples taken at four week intervals were tested for nucleophagocytic activity by mixing with the buffy coat layer of blood from the original patient and examining smears

The first preparation from plasma drawn at four weeks showed abundant nucleophagocytosis the engulfing cells almost always being polymorphonuclear neutrophils rather than histiocytes Some engulfed nuclei showed clear chromatin patterns similar to the tart cell Others showed varying loss of this pattern with a tendency to produce homogeneous inclusion bodies like those of LE cells A few cells had varying degrees of karyorrhexis of the nuclei and resembled the pre LE cell There were numerous clumps of polymorphs with in some cases apparent nuclear material occupying a central position in the clump

Preparations with plasma drawn at 8 12 16 and 20 weeks showed little or no nucleophagocytosis but markedly fragmented and conglutinated polymorphonuclears with a few cells showing karyorrhexis Some polymorphonuclears contained erythrocytes No adverse effect was produced in the

(8) Blood 8 651 654 J ly 1953

rule there was rebuilding of 2 000 2 500 ml blood in three weeks for periods of one to two years Subjective improvement was reported after two or three weeks treatment the patients usually feeling better in the few days after venesection than when the blood had regained its former levels In two patients who had been bled sufficiently to mobilize tissue iron liver size and hardness decreased and biopsies showed diminution of or as in one case complete disappearance of iron In all patients the complexion became lighter and in those with abnormal liver function or diabetes these also improved

Similar results have been reported in the literature in nine cases a detailed study gave complete corroboration

Whether the presence of iron in the tissues is injurious is undecided but there is undoubtedly a greater incidence of primary hepatic cancer in patients with hemochromatosis than in those with cirrhosis The clinical improvement that follows removal of iron from the tissues in these cases is also suggestive This therapy cannot be used when hemochromatosis is associated with anemia the procedure requiring a sound hemopoietic system and good general constitution [i e bleeding would make a refractory anemia worse —Ed]

Hematologic Response to Epinephrine Injection of this drug into normal and diseased subjects produces an increase of circulating leukocytes but the effect on red cell and platelet levels is less constant Patients with hypersplenic syndrome have been said to show a specific response to epinephrine the original leukocyte depression being attributed to abnormal splenic sequestration Some observers however have failed to demonstrate this abnormal response in suitable patients and further it has been shown that splenectomized subjects respond normally to epinephrine

Victor W Groisser and William Ruberman[3] (Brooklyn) carried out 47 epinephrine tests on 35 patients 9 had normal hemograms and the others a variety of hematologic disorders including splenomegaly in 21 All subjects had a prompt increase of all white cell elements maximal response occurring 5 30 minutes after injection No immature cells were noted except when they had been present beforehand In the second phase (two to four hours) lymphocyte count fell to preinjection levels while the neutrophil levels remained elevated In

(3) J Lab & Cl Med 43 386-394 Ma h 1954

At autopsy the liver weighed 3 900 Gm and was coarsely nodular There were two small pale circumscribed areas composed of irregular liver cells Elsewhere there was severe portal cirrhosis with heavy hemosiderin deposition in both liver cells and macrophages No iron was seen in the pale nodules Spleen weighed 1 000 Gm The capsule was thickened and there were large areas of dense fibrosis Iron was present in fairly large masses mostly extracellular The pancreas was fibrosed and contained iron deposits Bone marrow lymph nodes heart and skin showed hemosiderosis the marrow being hyperplastic.

Accumulation of iron in this patient resulted from excessive intestinal absorption, the seven blood transfusions during the last two years of life contributing little iron Anemia was probably due to a defect of incorporation of iron into the red cells at the same time stimulating the absorption of iron and thus being the primary etiologic factor Iron deposition in the spleen was probably due to production of Gamna Gandi bodies associated with portal hypertension

[Since hemochromatosis develops *without* iron therapy it is not certain that the iron here given therapeutically was *primarily* responsible —Ed]

Treatment of Hemochromatosis by Massive Venesection is described by W D Davies Jr and W R Arrowsmith[2] (Tulane Univ) In view of apparent lack of an excretory mechanism for iron phlebotomy seems a rational way to mobilize the excessive tissue iron in hemochromatosis

Of 10 patients with hemochromatosis diagnosed by liver biopsy 6 were selected for treatment by venesection Of the four excluded one had hepatic cancer one cancer of the prostate and two severe anemia The treatment involves removal of 500 ml blood daily until the hemoglobin level reaches 10 5 11 5 Gm /100 ml hematocrit about 35% Cells and plasma are separated and the plasma is replaced at each second venesection Thereafter venesection is done at four to eight day intervals depending on the hemoglobin level Multiple vitamins are given and insulin when required Aluminum hydroxide gel is given to control the gastrointestinal pH to ensure that all iron present is in the ferric form The usual diet for hepatic disease is rich in protein and so contains adequate phosphorus

One patient died of hepatic carcinoma shortly after treatment was started and another because of poor cardiac state and weakress probably received inadequate treatment Patients showed a remarkable tolerance for bleeding and as a

(2) A n Int Med 39 723 734 O tob r 1953

does not protect the nervous system and its use in this disease is dangerous Only in the rare disorders achrestic anemia and refractory megaloblastic anemia the uncommon megaloblastic anemia of infancy and pernicious anemia of pregnancy and some cases of sprue idiopathic steatorrhea and nutritional macrocytic anemia is folic acid of value Most megaloblastic anemias seen in this country require vitamin B_1 rather than folic acid and since in some cases the latter may be danger ous the use of mixtures of vitamin B_{12} and folic acid is un wise

Only in the aforementioned diseases is the use of liver extracts vitamin B_{12} or folic acid justified for they have no effect on the anemias of infection malignancy renal disease or leukemia Nor has iron unless these conditions are com plicated by blood loss to the extent of producing an iron de ficiency Blood transfusion is useful but only as a temporary measure and therapy should be aimed at the cause of the anemia if possible Particularly is this the case in scurvy and hypothyroidism

These agents are ineffective in hemolytic anemia but in congenital hemolytic anemia splenectomy is a well established measure and is also useful in some cases of the acquired form In the latter hormones may also be helpful but apparently only as they influence the underlying disorder

There is no evidence that the B vitamins other than folic acid and B_1 are of use in anemia Thiamine is only remotely concerned in erythropoiesis and riboflavin plays only a minor part Liver extracts stomach liver digests yeasts and other similar products do not yield in treatment of anemia any thing more than vitamin B_{12} or folic acid Nothing is gained by supplementing iron by other minerals the value of copper and cobalt therapy still having to be proved

Iron vitamin B_1 folic acid ascorbic acid and desiccated thyroid are specific remedies but there is no indication for the use of other vitamins and minerals commonly offered in shotgun mixtures Some conditions such as aplastic anemia and the anemia of renal disease cannot be treated specifically and the aforementioned accredited remedies are valueless In discriminate medication is to be deplored since it may cause loss of valuable confirmation of a diagnosis dependent on response to specific therapy

most cases the neutrophils did not show a continuous rise during this period The leukocyte response of the patients with hematologic conditions with or without hypersplenism showed no distinctive pattern Six patients three of whom had hypersplenic leukopenia were studied before and after splenectomy and three others two of whom had hypersplenic leukopenia were studied after splenectomy only A similar wide variation of leukocyte response was noted In three patients with aplastic anemia there was a marked percentage increase of all leukocytes due to lymphocytosis the neutrophils showed a lower than average increase Second phase response was similar to the normal in all cases The lymphopenia attributed to adrenal cortical stimulation was exaggerated in three patients with Addison's disease the mean decrease was 46% compared with the normal of 15%

After injection of epinephrine hemoglobin variably increased up to 3 Gm /100 cc but there was no distinctive pattern Platelet studies on 12 patients showed low levels in 6 and normal counts in 6 A maximal increase of 150 000 platelets was noted in a patient with myelofibrosis and myeloid metaplasia but otherwise changes observed were insignificant

Leukocyte response to epinephrine appears to depend little on the spleen but is probably based on a redistribution of cells from peripheral and visceral capillary beds by muscular contraction and increased blood velocity brought about by the drug Since it is apparently unrelated to abnormal splenic function this response is unlikely to be of value in the differential diagnosis of leukopenia with splenomegaly A low neutrophil response however may strengthen a diagnosis of primary marrow failure

Shotgun Antianemic Therapy is discussed by Maxwell M Wintrobe[4] (Univ of Utah) Iron therapy is effective in iron deficiency anemia except in prophylaxis of iron deficiency iron has no other medical value It is effective orally and well tolerated when given properly Rarely is parenteral administration required

Liver extract apparently because of its vitamin B_{12} content is effective in certain macrocytic anemias and related disorders characterized by megaloblastic marrow Folic acid can produce a hemopoietic response in pernicious anemia but

(4) Am J Med 15 141 142 August, 1953

mental hemolytic anemia erythroblastosis fetalis and acquired hemolytic anemia As the hemolysin titer is usually low or absent this mechanism alone is probably not responsible for the red cell destruction

The phenomenon of sludging seems to be more closely related to rouleau formation than to intravascular agglutination

[Not mentioned by the authors is the *indirect* hemolytic effect of red cell agglutination first indicated in 1940 by Ham and his associates as a cause of red cell intravascular stasis In 1950 those workers demonstrated the importance of injurious substances of ischemic tissue origin in causing hemolysis and increase in osmotic and mechanical fragilities of red cells They showed that immune anti red cell serums *do not* and autolyzing tissues *do* reproduce in vitro these effects on normal red cells The article by the present authors contributes important support to their hypothesis —Ed]

Syndrome of High Titer Cold Hemagglutination is described by M G Nelson and R J Marshall[6] (Royal Victoria Hosp Belfast) Cold agglutinins in very high titer sometimes appear suddenly in the serum of patients with no recent history of disease These antibodies persist and are associated with a long illness characterized by Raynaud s phenomenon gangrene hemolysis hemoglobinuria and anemia Two cases are reported

CASE 1 —Man 47 noticed that his hands became numb and blue at times during the winter and that after these attacks he passed black urine He had no history of serious illness and previously had been able to work in cold conditions Results of physical examination were negative

After the hand were exposed for 25 minutes to an outdoor temperature of 5 5 C they became blue and numb Samples of blood were collected hourly after exposure The first specimen but no subsequent ones showed marked hemoglobinemia Hemoglobinuria followed and was maximal at two hours Blood taken from the arm after it had been immersed 15 minutes in cold water showed free hemoglobin Ice applied to the conjunctiva caused slowing of the blood in the vessels with fragmentation of the flow small clumps of cells alternating with stretches of clear plasma The circulation became normal when the part was warmed Blood tests revealed normal red cell fragility and the reaction to the Coombs test was strongly positive Cold agglutinins in the serum reached a titer of 1 20 480 in saline at 0 C and of 1 327 680 in albumin The activity fell sharply between 10 and 20 C Agglutinins were absorbed on to the red cells when serum was separated below but not at 37 C The antibodies could be eluted from the cells by washing with warm saline but the washed cells still gave a positive Coombs reaction thus demon

(6) B it M J 2 314 317 A g 8 1953

Direct Observations of Intravascular Agglutination of Red Cells in Acquired Autoimmune Hemolytic Anemia are reported by Curt Wasastjerna William Dameshek (New England Center Hosp) and Zacharias D Komninos[5] (Tufts College) The appearance of blood as it streams through the capillaries under normal conditions is often different from that in pathologic states In the capillaries of a normal subject the blood stream appears homogeneous because the single red cells are free but in some pathologic conditions the red cells often seem to adhere to each other and thus present a granular or clumped appearance By slit lamp microscopy blood flow in the superficial vessels of the conjunctival scleras of 15 healthy persons and 53 patients with hematologic disease was studied Intravascular clumping was noted in 14 patients with autoimmune hemolytic anemia Agglutination was slight to moderate in patients who were in good clinical remission and marked in those with active hemolytic anemia In cases of hemolytic anemia associated with defect of the red cells Coombs test results being negative there was no agglutination or at most only fine granularity of the streaming blood even when anemia was severe Patients with leukemia or other malignant blood diseases had a varying degree of intravascular red cell agglutination

The life span of red cells is shortened in chronic leukemia though to a lesser extent than in acquired autoimmune hemolytic anemia Therefore the fact that intravascular red cell agglutination is also seen in these conditions does not preclude the hypothesis that intravascular red cell agglutination plays a role in the mechanism for destruction of red cells in immunohemolytic anemia As intravascular agglutination is not more pronounced in acquired hemolytic anemia than in other ill patients it seems likely that red cell agglutination is merely one of several mechanisms that shorten the life span of red cells Erythrocytic clumps probably suffer injury in the circulation through mechanical trauma and many of them are equestered in the spleen and other organs Another mechanism is undoubtedly phagocytosis of red cells noted in experi

(5) J Lab & Cl Med 43 98 106 J ry 1954

incriminate a cold hemolysin [Our experience favors the former explanation —Ed]

Treatment is unsatisfactory The most effective measure consists in avoiding exposure to cold Corticotropin urethane and vasodilator drugs were tried in the reported cases without effect

Acquired Hemolytic Anemia With Special Reference to Antiglobulin (Coombs) Reaction J V Dacie (Postgrad Med School London) carried out studies including direct and indirect antiglobulin tests on 18 patients with acquired hemolytic anemia

TECHNICS —For the direct antiglobulin test the patient s red cells were collected and washed three times in a large volume of warm saline A drop of each of a series of fourfold dilutions (1 4 to 1 1 024) of antiglobulin serum was placed serially on a tile and a drop of 10 15% suspension of red cells to be tested was added to each The drops were well mixed the tile was rocked gently and agglutinations were read after five minutes

For the indirect antiglobulin test sensitizations in patients serum were carried out with carefully screened red cells which would not react with any specific isoantibody which might be present Thus the reactions observed were thought to represent reactions between normal red cells and antibodies of acquired hemolytic anemia. The sensitized red cells were washed twice in warm saline and tested with antiglobulin serums Sensitizations were also carried out in acidified serums The pH of the mixture was about 6 5 Sensitizations were similarly carried out in acidified and unacidified serums previously inactivated by heating at 56 C for 30 minutes

For the gamma globulin neutralization test antiglobulin serum previously diluted to 1 4 in saline was added to equal volumes of fourfold dilutions of 3 8% solution of human gamma globulin After five minutes the series of neutralized or partially neutralized samples of antiserums were used to agglutinate sensitized red cells on a tile.

Antibodies of the warm type were demonstrated in 11 patients of whom 9 had idiopathic chronic acquired hemolytic anemia and 2 hemolytic anemia with lymphoblastic lymphoma and chronic lymphatic leukemia respectively Cold agglutinins were present in normal or just above normal titers The antiglobulin reaction was positive in 9 of 10 cases at 37 C and was not enhanced at 20 C it was not greatly inhibited by previously heating the serum Acidification increased the degree of sensitization but not strikingly so In most cases added gamma globulin inhibited the reaction but the effect was less marked in others and was not constant in

(7) Blood 8 813 823 S pt mb 1953

strating the presence of an incomplete cold antibody No cold hemolysins were detected and the Donath Landsteiner reaction was repeatedly negative as were serologic tests for syphilis

Case 2—Man 40 noted that during cold weather the hands became numb and painful During one cold spell the tips of both index and little fingers became dry black and painful (Fig 50) The skin was blue and atrophic Light touch and pinprick were not appreciated but arterial pulsation was good Five days after amputation of the finger tips digital ischemia developed which was relieved by immersing the hands in warm water Blood from a limb



Fg 50—Symm t i l d g t l gang (C tesy of N ls n M G a d M h ll R J B t M J 2 314 317 A g 8 1953)

immersed 15 minutes in chilled water contained large amounts of free hemoglobin and possibly a trace of methemoglobin mixed with methemalbumin Chilling the conjunctiva had the same effect as in Case 1 Serologic tests for syphilis were negative Cold agglutinins were present in a titer of 1 20 480 in saline and 1 81 920 in albumin and were most active between 0 and 10 C The Coombs test was positive but no cold hemolysins were found The Donath Land teiner reaction was equivocal

Exposure to cold causes intravascular agglutination and also hemolysis which is probably local intravascular stasis in the small vessels further lowering the local temperature Minute thrombi may form in the vessels distal to the blocked area Some workers believe that cohesion of red cells in motion is sufficient to destroy them because of the increased mechanical fragility of the agglutinated cells whereas others

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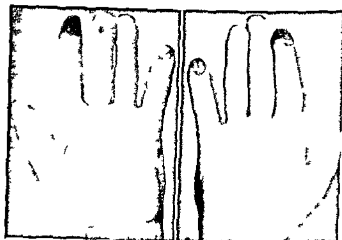
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two or was of intermediate type Serial observations were carried out for two years in one case The patient is now in remission although the antiglobulin reaction remains positive The character of the antibody has changed the reaction previously inhibited by gamma globulin has recently become less affected by it A well marked zone of inhibition was usually seen when sensitized cells were suspended in high concentrations of antiglobulin serum this being true of all cases in which the antibody was thought to consist of gamma globulin Zoning was less obvious when there was evidence that the antibodies were formed at least in part of globulins other than gamma

Nine of 10 serums irreversibly agglutinated trypsinized normal red cells three caused lysis also One unacidified serum lysed cells from paroxysmal nocturnal hemoglobinuria patients at 37 C Thus the indirect antiglobulin test and trypsinized red cell technic seem to be equally valuable in demonstrating warm antibodies

Of seven patients with cold agglutinins four had idiopathic chronic acquired hemolytic anemia one hemolytic anemia with reticulosarcoma and two hemolytic anemia following virus pneumonia Cold agglutinin titers at 2 C were high for all patients and direct antiglobulin tests were positive with little or no inhibition at the highest concentrations of antiglobulin serum All reactions were only slightly inhibited by added gamma globulin Indirect antiglobulin reactions were positive at 20 C and in six were positive at 37 C but usually much weaker Acidification of the serum in all but two instances greatly intensified the reaction whereas previous heating of the serum completely prevented it Two serums seemed to contain both warm and cold antibodies but inactivation tests proved the sensitizing antibody to be the cold one

Separation of warm and cold antibodies has little clinical correlation Warm antibodies were found in most idiopathic cases and cold antibody in hemolytic anemia following virus pneumonia as well as in some cases of the idiopathic disease Splenectomy was followed by sustained remissions in idiopathic cases of both warm and cold antibody types

Although sensitization by cold antibody to antiglobulin serum depends on thermolabile serum components other work has shown that it also requires the presence of thermostable components Absence of zoning and the relation

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[This report will be of particular interest to those concerned with immunohematology —Ed]

Specificity of Autoantibodies in Acquired Hemolytic Anemia Until recently it was assumed that the antibodies found in acquired hemolytic anemia were nonspecific and unrelated to any known blood group antibodies The discovery of anti C and anti e in the serum of a patient with hemolytic anemia led J V Dacie and Marie Cutbush[8] (Postgraduate Med School London) to reinvestigate nine other cases of acquired hemolytic anemia in which warm autoantibodies had been considered nonspecific

Red cells from each of the 10 patients gave a positive reaction to the direct Coombs test and a prozone was observed when the cells were tested against serial dilutions of a highly potent antiglobulin serum Agglutination was readily inhibited by adding small amounts or human gamma globulin to the antiglobulin serum In eight cases Rh genotypes had been determined All patients had received blood transfusions during their illness Serums were tested for agglutination of trypsinized red cells and sensitization of red cells to antiglobulin serum When possible eluates were prepared from the patients red cells and tested for antibodies Serums and eluates were also absorbed with red cells of different genotypes and tested against a panel of cells

In only one case the original did the serum fail to react with cDE/cDE and –D–/–D– cells but this serum agglutinated the patient s own red cells and cells containing antigens e or C That the serum did contain anti-e was confirmed by tests on red cells from persons of known genotype who lacked C antigen after absorption of anti e the presence of anti C antigen was also demonstrated Serum of all other patients reacted with all samples of cells and apparently contained nonspecific antibodies In some cases the reactions were notably more active against cells of particular genotypes thus suggesting that specific antibodies were also present These appeared to be of two types immune isoantibodies probably the result of previous transfusions (e g the anti E noted in four patients) and autoantibodies directed against the Rh

(8) J Cl n P th 7 18 21 F bru ry 1954

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[This report will be of particular interest to those concerned with immunohematology —Ed]

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Red cells from each of the 10 patients gave a positive reaction to the direct Coombs test and a prozone was ob served when the cells were tested against serial dilutions of a highly potent antiglobulin serum Agglutination was readily inhibited by adding small amounts or human gamma globulin to the antiglobulin serum In eight cases Rh genotypes had been determined All patients had received blood transfusions during their illness Serums were tested for agglutination of trypsinized red cells and sensitization of red cells to antiglo bulin serum When possible eluates were prepared from the patients red cells and tested for antibodies Serums and elu ates were also absorbed with red cells of different genotypes and tested against a panel of cells

In only one case the original did the serum fail to react with cDE/cDE and -D-/-D- cells but this serum aggluti nated the patient s own red cells and cells containing antigens e or C That the se um did contain anti e was confirmed by tests on red cells from persons of known genotype who lacked C antigen after absorption of anti e the presence of anti C antigen was also demonstrated Serum of all other patients reacted with all samples of cells and apparently contained non specific antibodies In some cases the reactions were notably more active against cells of particular genotypes thus sug gesting that specific antibodies were also present These ap peared to be of two types immune isoantibodies probably the result of previous transfusions (e g the anti E noted in four patients) and autoantibodies directed against the Rh

(8) J Cl n. P th 7 18 21 F bru ry 1954

system (anti e + anti C in one case anti e + anti D in one and anti e in three cases)

Of the nine patients in whom nonspecific antibodies were present three had an additional nonspecific antibody absorbed by all types of cells except -D / D This suggests that -D / D lacks an antigen other than c C e or E

Long Term Picture in Autoimmune Hemolytic Disease Lawrence E Young and Gerald Miller[9] (Univ of Rochester) report representative cases from a group of 23 9 of which have been observed for 3 22 years

CASE 1 —Woman 56 had six episodes of acute hemolytic anemia over four years after the initial attack for which splenectomy was performed Each attack was accompanied by spherocytosis increased osmotic and mechanical red cell fragility and increased serum bili rubin concentration and fecal urobilinogen excretion Abrupt changes in hemolytic activity were not accompanied by abrupt changes in autoantibody titer In quiescent periods the red cells remained strongly agglutinable by antiglobulin serum The second relapse (Fig 51) after splenectomy followed cholecystectomy but subsequent episodes have no particular association Thrombophlebitis has been a trouble some complication Cortisone was given during each of the last four attacks with good effect The first two relapses terminated abruptly without hormone therapy

CASE 2 —Woman at age 34 had splenomegaly anemia and leukopenia (1931) During the next 18 years the spleen gradually increased in size anemia and icterus recurred at irregular intervals The white cell count was often between 1 300 and 3 000/cu mm and there was persistent thrombocytopenia Splenectomy in 1949 was fol lowed by a good hematologic response

This is more than a case of hypersplenism as incomplete autoantibodies were demonstrable in the serum more than two years after operation

CASE 3 —Woman first seen at age 58 had no relapse despite a slow initial response after splenectomy and a persistent positive Coombs reaction seven years later

CASE 4 —Man first examined at age 23 had purpura spleno megaly thrombocytopenia and leukopenia but soon began to feel well Despite increasing splenomegaly there was no recurrence of symp toms for nearly six years when an acute hemolytic episode devel oped The subsequent course was unfavorable Many features sug gested periarteritis nodosa but biopsy of muscle liver and spleen showed no distinctive lesions

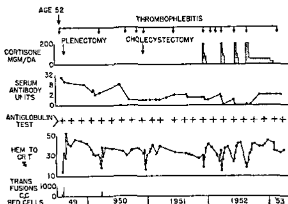
This type of anemia may complicate diffuse collagen dis eases but the history of this case is unusual

CASE 5 —Woman age 61 when first seen had hemolytic anemia

(9) Tr A Am. Phy ci s 66 190 199 1953

on at least four occasions over eight years before reticulum cell sarcoma was diagnosed Re examination of sections of spleen re moved seven years before death revealed lymphoid hyperplasia but not enough to justify a diagnosis of lymphoma at that time There was a spontaneous remission with a persistent positive reaction to the direct Coombs test during the following quiescent four years Complement titer was extremely low during the last five years and cryoglobulinemia appeared in the last six months of life

CASE 6—Woman age 47 when first seen had chronic lympho cytic leukemia for five years before hemolytic anemia appeared



F g 51—S rum nt b dy t e p l f d l t f p t ent m p od g 50% ggl t t f tryp t t d n m l ythr yt (50% d p t dete m d by method f Heden) (C rt y f Y g L E nd M ll G T A Am Phy s 66 190 199 1953)

Hemolysis was promptly reduced and a partial remission of leukemia occurred after the first two courses of ACTH given nearly a year apart In the last two years of life cryoglobulin was found in the serum in concentrations up to 1 2 Gm /100 cc

CASE 7—In a man first seen at age 63 hemolytic anemia first appeared as a complication of chronic lymphocytic leukemia The first attack began to subside after splenectomy but recurred in a few months followed by thrombocytopenia He recovered and remained well until a cerebral hemorrhage occurred three years later No treatment was given and there was no recurrence of anemia al though the reaction with the antiglobulin test remained positive

In more chronic cases hemolytic episodes may recur at irregular intervals over many years Of 16 patients treated with cortisone or ACTH 9 have maintained remission with *out hormone therapy* Leukopenia or thrombocytopenia may precede accompany or follow attacks and reports suggest

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showed evidence of jaundice and indicated liver damage Pyrexia increased and on the 10th day the hemoglobin level was 7 5 Gm A transfusion of 500 ml blood was given By the 21st day bili rubinemia had subsided the hemoglobin level was 12 Gm and heterophil antibody titer 1 1 792 though reaction to the direct Coombs test remained positive After six weeks the patient was discharged with a negative heterophil antibody titer and Coombs reaction normal liver function tests and a hemoglobin level of 13 5 Gm

CASE 2—Man 33 had jaundice and sore throat with enlarged axillary cervical and inguinal lymph nodes Blood examination showed 9 000 lymphocytes/cu mm of which most were atypical a hemoglobin level of 14 5 Gm /100 cc and 4 200 000 red cells/cu mm Serum bilirubin was 4 22 mg /100 cc Cephalin cholesterol floccula tion was strongly positive and the heterophil antibody titer unab sorbed was 1 7 During the second week the jaundice intensified and the hemoglobin level fell to 8 Gm There were 12% reticulocytes with many spherocytes Results of the direct and indirect Coombs tests and the trypsin treated red cell test were negative The hetero phil antibody titer was 1 224 on the 10th day but fell thereafter After three weeks the hemoglobin and red cell values began to rise and the patient was discharged at 10 weeks

CASE 3—Youth 19 a Negro had headache fever and jaundice with splenomegaly Blood examination showed atypical lymphocytes hemoglobin level 14 Gm /100 cc red cells 3 900 000/cu mm and a negative test for sickling Serum bilirubin was 5 4 mg /100 cc and cephalin cholesterol flocculation was strongly positive Heterophil antibody titer was 1 896 The icterus increased and hemoglobin fell to 10 Gm Reticulocytes were 14% with spherocytosis and the direct and indirect Coombs tests were negative but the trypsin treated red cell preparation was positive Hemoglobin level fell to 8 5 Gm at the 7th day but by the 21st day began to rise spon taneously

In these cases the reactions to the Coombs and trypsin treated red cell tests were variable but spherocytosis reticu locytosis jaundice and marrow erythroid hyperplasia were common to all The jaundice was more intense than in the usual patient with primary acquired hemolytic jaundice or uncomplicated infectious mononucleosis Treatment should be expectant except when the degree of hemolysis warrants transfusion or cortisone therapy Successful splenectomy has been reported in one case

Aplastic Crisis in Congenital Hemolytic Icterus (Acholuric Jaundice) Description of Three Cases J Margolis[2] (Royal Alexandra Hosp for Children Sydney) observed

(2) M J A t l 2 100 103 J ly 18 1953

that immune mechanisms may be involved in destruction of white cells and platelets Autoimmune hemolytic anemia may be the first manifestation of a disorder of reticuloendothelial or collagenous tissues Viremia as a factor has been suggested but virus isolation studies in nine cases of the present series were negative Red cells have often remained strongly agglutinable and autoantibody has frequently been demonstrated during quiescent periods Therefore factors other than concentration of antibody must be concerned in the destruction of red cells

Some doubt has been expressed as to whether the autoantibodies in the serum and attached to the red cells really are antibodies Globulin eluted from the stroma of these red cells behaves electrophoretically like gamma globulin and has reacted with normal red cells as do some incomplete isoantibodies such as anti Rh Warm serum panhemagglutinins of some patients have also reacted like incomplete isoantibodies except for a difference in the effect of pH

Serologic findings together with complement deficiency and cryoglobulinemia suggest that abnormalities of plasma proteins may play a prominent part in the disease Abnormal electrophoretic patterns of gamma globulins have been seen in some cases and in 16 of 20 cases the small amount of hemoglobin in the plasma showed distinctly abnormal mobility This does not imply that the hemoglobin is necessarily abnormal In other cases abnormal alpha globulins have been demonstrated there being either a deficiency or failure to increase in response to infection

[This report represents a valuable contribution to modern clinical descriptions of acquired hemolytic anemia —Ed]

Hemolytic Anemia Complicating Infectious Mononucleosis Report of Three Cases, observed among 62 cases of infectious mononucleosis is made by Melvin L Samuels [1]

Case 1 —Youth 20 had low grade fever malaise and later jaundice with large urticarial lesions over chest and back Cervical lymph nodes were enlarged Blood examination revealed numerous atypical monocytoid leukocytes and there was moderate anemia the hemoglobin level being 9 Gm /100 cc and the red cell count 2 300 000/cu mm There were 15% reticulocytes and a positive reaction to the direct and indirect Coombs tests Trypsin treated red cells were negative Heterophil antibody titer was 1 7 168 and the bone marrow showed erythroid hyperplasia Liver function tests

(1) U.S Armed For M J 4 1778 1782 D c mb 1953

demonstrated to follow infections in other types of hemolytic anemia such as sickle cell anemia. Critical studies show that this occurs even in normal subjects as an otherwise clinically occult phenomenon True hemolytic crises accompanied by increase of anemia reticulocytes and icterus also occurs in congenital hemolytic icterus and sometimes also following an upper respiratory infection —Ed]

ACTH and Cortisone in Treatment of Acquired Hemolytic Anemia Report of Four Cases Henning Letman[3] obtained satisfactory results in treating four patients with immunohemolytic anemia with ACTH and cortisone Two had recurrences after short courses of treatment but a remission was maintained by a daily dosage of 50 mg cortisone which has now been withdrawn for three months without relapse Two patients seem to have completely recovered after a short course of combined therapy

Woman 64 had a history of fatigue for six months She had been treated for anemia with liver and iron without benefit Examination showed slight jaundice and an enlarged spleen The hemoglobin content was 5 2 Gm /100 cc and the serum bilirubin level and reticulocyte count were increased The bone marrow showed normoblastic hyperplasia A direct Coombs test was positive and an indirect Coombs test negative The patient s red cells showed spherocytosis and increased fragility and were slightly agglutinated by her own serum in normal serum and in saline She was given 40 units of ACTH daily for 10 days The tendency of the red cells to spontaneous agglutination disappeared but no other improvement was noted For seven days 100 units of ACTH were given daily followed by a course of cortisone the initial daily dose of 200 300 mg being later decreased Complete remission occurred but a relapse followed after three weeks ACTH and cortisone therapy was resumed with prompt remission and the patient was maintained on a daily dose of 50 mg cortisone for 212 days Three months after cessation of treatment she was still in remission Titers of the direct Coombs test fell gradually during treatment and red cell fragility fluctuated with the do e of corti one Enlargement of the spleen disappeared during maximal cortisone dosage but reappeared as dosage was reduced It has not reappeared since ces ation of therapy

The other patients were a woman 74 with similar history clinical features and response to therapy a boy 15 in whom a short course of ACTH caused an apparently tenable remission observed for 12 weeks since cessation of therapy and a boy 5 who responded to ACTH and cortisone by a remission which so far has lasted 4 weeks

During therapy decrease in Coombs test titers was gradual and difficult to evaluate The tendency (noted in three

(3) Act med sca d v 146 436-447 1953

acute hemolytic crises in three patients aged 4 6 and 8 the only siblings of a family affected by acholuric jaundice on the mother s side Although symptomless the mother had well marked spherocytosis and increased fragility of the red cells and a 15% reticulocyte count The maternal grandfather and a maternal aunt both had the disease

The first patient a boy aged 6 had severe anemia and a palpable spleen six weeks after an attack of gastroenteritis A provisional diagnosis of acute leukemia was made Marrow puncture revealed gross depression of red cell precursors but a repeat puncture six days later showed an active normoblastic marrow Hemoglobin levels of his two sisters were found to be normal but they were prevented from returning for further tests by onset of illnesses which proved to be acute crises The earliest marrow specimens were obtained from these patients about the 10th day of the illness and in both instances showed early active normoblastic hyperplasia the appearance cor responding to maturation arrest and probably representing transition from aplastic to active marrow In the three cases hematologic studies yielded all the findings of acholuric jaun dice Treatment by transfusion was followed by uneventful recovery

From these case histories may be drawn a composite pic ture of sudden cessation of erythropoiesis precipitated by some external disturbance probably an infection followed by disappearance of red cell precursors from the marrow In view of the abnormally short life span of spherocytes the dis appearance of 75% of the red cells from the circulation as occurred in two patients is not unexpected On the 7th or 8th day in response to the severe anemia rapid regeneration occurs in the marrow but not until the 12th day when the normoblasts are mature is reticulocytosis observed in the peripheral blood

The beneficial effect of splenectomy in this disease need not implicate the spleen etiologically since the life span of the spherocytes is greatly prolonged after this treatment and a sudden marrow aplasia would not result in such a severe anemia Perhaps the agent or agents responsible for acute crises in these patients have a similar effect on the marrow of normal persons The nature of such agents is not clear but evidence points to an infection possibly viral

[Manifest temporary suppression of erythropoiesis has indeed been

corpuscular hemolytic component in this disease depends on an immunologic mechanism related to multiple transfusions However circulating antibodies were not demonstrated by Lichtman and his co workers by the Coombs test or enzyme treated red cells Persistent splenomegaly suggested the possibility that an abnormal splenic function was involved in the hemolytic process

Splenectomy was carried out on each patient In four of five observed for longer than six months transfusion requirements fell significantly to 19 21 3 28 3 and 30% of the preoperative figures The fifth patient showed no improvement in transfusion requirements In two survival time of transfused normal red cells was measured It was normal in one but only slightly increased toward normal in the other the patient not benefited by operation

In this selected group of patients i e with an extracorpuscular hemolytic component splenectomy was of value in most instances This suggests that chronic splenomegaly of at least three years duration played some part in the rapid destruction of the transfused red cells The only patient who did not improve after splenectomy showed the greatest degree of hepatomegaly which suggests that the spleen may not be the only organ involved in the hemolytic process

Extracorpuscular hemolytic component should be suspected when the transfusion requirements unexplainedly increase though the temporary variations in endogenous hemopoiesis which occur in thalassemia major should always be borne in mind

[Thus splenectomy may be more valuable in thalassemia than was previously considered to be the case —Ed]

↓ The next four articles discuss clinical genetic and constitutional aspects of sickle cell disease that can now be distinguished —Ed

Two Cases of Sickle Cell Disease Presumably Due to Combination of the Genes for Thalassemia and Sickle Cell Hemoglobin are described by James V Neel Harvey A Itano and John S Lawrence[5] Sickle cell anemia was diagnosed in a woman 36 of Greek descent with recurrent episodes of fever and jaundice persistent anemia and a positive sickling test A family study included both parents five siblings two nieces one nephew and the patient s husband and son Sickle cell trait was exhibited by the mother one sister and the

(5) Blood 8 434 442 M y 1953

cases) to spontaneous agglutination of red cells in the patient s serum, normal serum and saline disappeared during ACTH therapy in two cases and was greatly diminished in the third though in this instance it persisted at low temperatures Acidification stimulated spontaneous agglutination Changes in osmotic fragility were small but there was distinct diminution during treatment with a transitory increase when the dosage was reduced

The beneficial effect of ACTH and cortisone is probably due mainly to an influence on the autoantibodies but the subsidence of splenic enlargement may, perhaps be responsible for a diminished destruction of red cells Although both antibodies and splenomegaly may return when treatment is stopped symptoms do not necessarily recur Patients who cannot be kept in remission by small doses of cortisone must undergo splenectomy after remission is satisfactorily achieved with ACTH or cortisone

Studies on Thalassemia I Extracorpuscular Defect in Thalassemia Major, II Effects of Splenectomy in Thalassemia Major with Associated Acquired Hemolytic Anemia Reported transfusion studies indicate that the hemolytic component in thalassemia major is a defect of the red cell Herbert C Lichtman R Janet Watson Felix Feldman Victor Ginsberg and Jean Robinson[4] have observed about 20 children with this disease all of whom required repeated blood transfusions at short intervals Before transfusion therapy hematologic levels had remained fairly constant Since there was no increased blood loss it seemed that the transfused cells were not surviving as expected or that endogenous hemopoiesis had been decreased in response to each transfusion or both

Seven patients aged 5 16 with thalassemia major were studied All were first noted to be anemic in infancy and presented a typical hematologic and clinical picture including splenomegaly In six survival time of transfused normal red cells was greatly shortened the destruction being apparently independent of the age of the red cells and thus implicating an extracorpuscular hemolytic component Other authors have reported normal survival time of transfused cells in seven patients with this disease but most were younger and had not received many transfusions It may be that the extra

(4) J Cl n In t 32 1229 1235 D mb 1953

cell hemoglobin in the patients described here might represent the amount of sickle cell hemoglobin usually present in the trait associated with diminished production of normal adult hemoglobin An absolute increase in the amount of sickle cell hemoglobin per erythrocyte as has been observed in *sickle cell hemoglobin C disease* is possibly compensatory and probably contributes to its preponderance in sickle cell thalassemia disease

The two siblings with sickle cell thalassemia disease differed from each other in the proportion of the types of hemoglobin especially in fetal hemoglobin proportions This phenomenon is possibly related to the age at which severe anemia occurs the fetal mechanism being reactivated if it has not been too long dormant There is however little relation between the proportion of alkali resistant component and the severity of the disease Differences in adult hemoglobin proportions have been noted and in these patients the differences in the various types may involve unrelated absolute variations

Reference to abnormal hemoglobins is probably best made by convenient descriptive terms such as fetal sickle cell or in the case of the newer hemoglobins by the letters C and D Until the genetic structure is established there must be a nonspecific nomenclature and substitution of arbitrary numbers offers little advantage

Further Studies on Hemoglobin C II Hematologic Effects of Hemoglobin C Alone and in Combination with Sickle Cell Hemoglobin are described by Eugene Kaplan Wolf W Zuelzer and James V Neel[6] (Univ of Michigan) Several distinct hematologic disorders are associated with the presence of the sickling gene One of these is sickle cell hemoglobin C disease which develops in offspring of parents one of whom carries the gene for sickle cell the other for hemoglobin C Study of seven Negro children has shown that it is a mild disease causing few specific complaints the hemolytic components being an inherited red cell defect Though occasionally the anemia is severe for a short period the disease interferes little with normal growth or activity Moderate hepatosplenomegaly present in early childhood usually persists beyond age 5 but later tends to subside Cardiac abnormalities and skeletal hypertrophy are rare

(6) Bl od 8 735 746 A gu t 1953

patient s son one brother had sickle cell anemia and the father and two brothers had thalassemia minor Occurrence of thalassemia minor in one parent and sickle cell trait in the other strongly suggests that the sickle cell disease of the patient and her brother was due to the combination of these genes Tests of ABO MN and Rh blood groups revealed no evidence of nonpaternity

Hemoglobins of the patient both parents and five siblings were examined by electrophoresis of carbonmonoxyhemoglobin in cacodylate buffer and in 0 01M Na_2HPO_4 and separation of alkali denatured hemoglobin was done The biochemical findings in the subjects with sickle cell trait and with thalassemia minor agreed with results of previous studies In those with sickle cell thalassemia disease (the patient and her brother) there was a preponderance of sickle cell hemoglobin 61 and 84% and alkali resistant residues comprised 19 and 5% of the hemoglobins The brother was found to have normal adult hemoglobin on electrophoresis in Na_2HPO_4 In these cases the proportion of sickle cell hemoglobin was higher than in the sickle cell trait but lower than in the most common type of sickle cell disease

Most cases of sickle cell disease develop in children whose parents have the sickle cell trait and thus rest on a homozygous basis The second most common type occurs when a child receives a sickling gene from one parent and a gene responsible for a poorly understood hemoglobin abnormality (hemoglobin III or C) from the other This has been called sickle cell hemoglobin C disease Hemoglobin C has more abnormal mobility electrophoretically than sickle cell hemoglobin and occurs in 6% of Negroes with sickle cell disease The third type is that described here and accounts for most cases in the Caucasian race and is particularly frequent in persons of Greek Sicilian or southern Italian derivation What appears to be a fourth type demonstrated so far only in one family involves a new gene responsible for a hemoglobin abnormality hemoglobin D combined with a sickling gene The disease is not associated with the sickling phenomenon but the hemoglobin has the mobility of sickle cell hemoglobin

Recent studies suggest that the primary action of the thalassemia gene is partially to block normal adult hemoglobin synthesis Therefore the increased proportion of sickle

salient differential features are given in Figure 52 Differential diagnosis from sickle cell anemia is readily made from the absence of a severe clinical course and the presence of large numbers of target cells Thalassemia major is a chronic illness with persistent marked splenomegaly severe hypochromic anemia no sickling or siderocytosis and far fewer target cells Thalassemia minor is usually an asymptomatic trait with infrequent slight splenomegaly minimal red cell changes and no sickling increase in siderocytes or large numbers of target cells Thalassemia may be further differentiated by hemoglobin electrophoresis

Filter Paper Electrophoresis of Human Hemoglobins with Special Reference to Incidence and Clinical Significance of Hemoglobin C Time labor and expense of large scale electrophoretic studies have hitherto restricted fuller investigation of the abnormal hemoglobins C and D Using filter paper electrophoresis Ernest W Smith and C Lockard Conley[7] were able to obtain considerable data concerning hemoglobin C

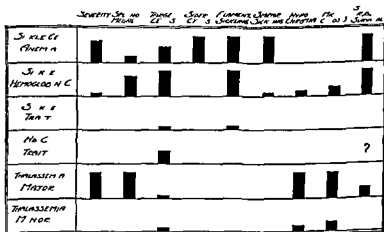
TECHNIC —Red blood cells from at least 0 5 ml blood are lysed by adding 1 volume of distilled water and ½ volume of toluene a final concentration of between 3 and 16 Gm /100 ml hemoglobin yielding good results Sheets of filter paper are supported between ¼ in glass plates and clamped to secure uniform pressure The plates are placed at each end of two buffer tanks partitioned to separate the electrode part from that containing the plate Electrodes were of platinum with a mercury contact A veronal® buffer pH 8 6 and about 0 06 ionic strength was used and 15 ma of current was passed through the apparatus from a power supply with a range of 150 450 volts and with a current flow of up to 200 ma A voltage drop of as little as 2 volts produced uneven migration and to avoid this buffer bridges were placed at opposite ends of the buffer tanks in compensation

Along a line in the center of the paper which had previously been wet with buffer 0 04 ml hemoglobin solution was placed and the lateral edges of the glass plates sealed to prevent evaporation Migration was evident within a few minutes separation was apparent within an hour and by two hours hemoglobins A S and C could be identified (Fig 53) These were widely separated at four hours but hemoglobin F was only distinguishable after five or six hours Hemoglobin of known abnormal composition was placed in the center as a reference

Of 500 white subjects screened none had S or C hemo

(7) B ll J h H pk H p 93 94 106 A gu t 1953

Hematologically in the cases studied there was a mild anemia with sickling and target cells hemoglobin levels being about 9 10 Gm /100 cc and the red cell count 3 500 000-4 500 000/cu mm The number of reticulocytes was frequently increased and the bone marrows showed erythroid hyper plasia Corpuscular constants indicated a definite microcytosis but as the cells were apparently normal in size and shape the decreased volume was probably due to abnormal thinness of the cells A striking feature was the large numbers 40 85% of target cells consistently present The number of siderocytes



F g 52 —H m tolog c p fil f c rt n h rit d ab rmal t es of blood Ea b b r ep t l t e d g ee f bn rm l ty fo gi en cha act ist c (C rtesy of Kapla E *et l* Blood 8 735 746 Augu t 1953)

was not increased Osmotic resistance was increased in every case mechanical fragility being normal in ordinary oxygen tension but increased in saturated carbon dioxide The serum bilirubin level was normal and jaundice was not noted in any patient though fecal urobilinogen excretion was increased in each of the three children so studied Transfused red cells had a shortened survival time

Data on 13 subjects with hemoglobin C trait showed only increased numbers of target cells 3 33% and the transfusion survival time of the red cells was shortened

Sickle cell hemoglobin C disease is sufficiently distinct from similar hematologic disorders to be easily recognized

salient differential features are given in Figure 52 Differential diagnosis from sickle cell anemia is readily made from the absence of a severe clinical course and the presence of large numbers of target cells Thalassemia major is a chronic illness with persistent marked splenomegaly severe hypochromic anemia no sickling or siderocytosis and far fewer target cells Thalassemia minor is usually an asymptomatic trait with infrequent slight splenomegaly minimal red cell changes and no sickling increase in siderocytes or large numbers of target cells Thalassemia may be further differentiated by hemoglobin electrophoresis

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globins D has mobility similar to S this can also be excluded Of 500 Negroes screened 8 4% had *hemoglobin S 9 had C* trait and 1 had C S combination giving a hemoglobin C inci dence of 2%

The nine C trait subjects and five more encountered in other studies showed no regular *hematologic or clinical* ab normality All except one were females and in only one an undernourished infant with no evidence of hemolysis was there anemia This responded to iron Blood smears of three



F g 53—M g t n du g elect ph b g n g f om d tt d l Dye g o t g n t y f r al t n w th h m gl b n t t o greater than 3% Wh tm n n 3 6 × 12 filt p pe 15 ma d 380 v lt w u d Hem gl b n A is fast st m g h m gl b n S h s t m d t m b l ty d hemo gl b n C m g ates mo t slowly H m gl b n F w s n t p t on ent t g e i r th n 5% f t tal of a y pot and t d mon t bl n th p p to (C t y of Sm th E W a d C l y C L B ll Joh Hopk H p 93 94 106 A gust 1953)

subjects showed no increase of target cells whereas smears of four others showed small but significant increases

The patient with the C S hemoglobin combination and six others were studied These patients usually have only mild anemia and no jaundice but hemolytic episodes may develop in which jaundice appears and anemia becomes profound Such episodes occurred in two patients during pregnancy Attacks of abdominal pain frequent in sickle cell anemia are unusual but two patients had episodes of gross unilateral hematuria and one had recurrent convulsive attacks Observations suggested

that splenomegaly not only persists into adult life but increases in degree Sometimes there is transient enlargement during hemolytic episodes Blood smears from all seven patients showed an increase of target cells which varied from 60 to almost 100% of the total red cells Mean cell diameter was above normal but mean cell thickness was reduced

Genetic studies indicate that hemoglobin C is inherited as a mendelian dominant character

Pregnancy and Sickle Cell Disease John Quincy Adams Frank E Whitacre and Lemuel W Diggs[8] (John Gaston Hosp Memphis Tenn) report on sickling tests done on 2011 Negro obstetric patients The sickle cell trait without anemia was observed in 7 9% This figure approximates the incidence of the trait in the local population The patients were not unduly susceptible to secondary anemia of pregnancy and their age gravity and parity compared closely with those of unselected Negro women Toxemia and fetal deaths were commoner in the patients with sickle cell trait but other obstetric complications were not increased

Tests on 824 babies born to these mothers showed sickling in 1 1% but none had sickle cell anemia including 3 infants of mothers with sickle cell anemia

During 1940 52 true sickle cell anemia was seen in 13 patients (25 pregnancies) For this period the incidence of sickle cell anemia was once in 2 075 deliveries an incidence much lower than that of the disease in the general Negro population Fertility does not seem to be affected by sickle cell anemia for women with this disease conceive initially at the age of normal women but usually do not live long enough to bear many children

Sickle cell anemia is aggravated by pregnancy the hemoglobin level often falls very low and the serum bilirubin level and reticulocyte counts are increased Except for hemorrhage all obstetric complications are more frequent Sickle cell anemia and hypertensive toxemias of pregnancy are both vaso obliterative disease and produce similar lesions such as thromboses and hypoxia Differentiation may be difficult but a severely anemic patient is in any case less able to overcome the etiologic factors of toxemia Contracted pelves are probably more common in sickle cell anemia because of faulty

(8) Ob t & Gy 2 335 352 Oct b 1953

bone development In the present series puerperal morbidity (pyrexia) was greatly increased postpartum endometritis being the most frequent cause Fetal mortality was increased there being only 13 live births (52%)

Although sickle cell anemia alone does not warrant sterilization this course may be considered when other factors such as toxemia severe anemia frequent crises and multiparity with sickle cell disease in the progeny arise

The tissue changes in pregnant patients with sickle cell anemia are essentially the same as those in uncomplicated sickle cell anemia except that pregnancy increases the probability of pelvic thromboses or pulmonary emboli Sudden death in pregnant patients with the sickle cell trait are characterized by blood vessels congested with sickled cells splenomegaly evidence of right heart failure and focal ischemic and hemorrhagic necroses The spleen is large dark and firm in contrast to the small atrophic siderofibrotic spleen in sickle cell anemia

Pregnancy is a definite hazard to a patient with either sickle cell trait or anemia Such patients should be under close surveillance and frequent hemoglobin estimations should be made and transfusions given if the anemia becomes severe Oxygen and routine antibiotics should be given during labor and parturition and in the immediate postpartum period Anesthetics and heavy sedation should be avoided as the slightest anoxia may cause intravascular sickling with dire results Local infiltration and block technics are the only safe measures

[However transfusions of normal i e non sickling red cells will effectively dilute the sickling tendency of the patient s blood under anoxic conditions —Ed]

Paroxysmal Nocturnal Hemoglobinuria Relation of Clinical Manifestations to Underlying Pathogenic Mechanisms is discussed by William H Crosby[9] (Walter Reed Army Med Center) Unlike other hemolytic diseases in which antibodies have been incriminated in paroxysmal nocturnal hemoglobinuria (PNH) a definite defect of the red cell has been demonstrated by incubation and transfusion experiments Although the plasma is probably normal it contains specific factors which destroy PNH red cells The hemolytic system comprises hemolytic factors and their inhibitors The most

(9) Blood 8 769 812 S ptembe 1953

important inhibitor is easily destroyed by thrombin thus al lowing increased hemolysis As a consequence any increased activity of the blood coagulation system in a patient may pro duce a hemolytic crisis Since no spherocytosis precedes hemolysis surface lipids are probably not involved Recent work suggests that the reaction is proteolytic and perhaps acts on the stromal protein Hemoglobin is of normal type and there is no increased fragmentation of red cells The basic lesion may lie not in the stromal protein but in the intracellu lar enzymes which sustain the cellular fabric

The spleen plays little or no part in PNH and splenec tomy is of little benefit and even carries a considerable risk of postoperative thromboses Hemolysis is intravascular and more or less continuous becoming more active during sleep When the plasma hemoglobin level tops the renal threshold hemoglobinuria occurs more remote sequelae being hemo siderinuria and abnormal iron metabolism Increased hemoly sis during sleep may be due to retention of CO with a mini mal fall in plasma pH or may be related to increased thrombic activity

After a blood transfusion PNH patients commonly have a reaction which is consistently followed by a hemolytic crisis during which the patient s own red cells are hemolyzed Later blood changes resemble Widal s hemoclastic crisis The blood coagulability increases and then in response to the secretion of a heparin like factor decreases During this period of activ ity the PNH hemolysis is inhibited only to reappear with increased intensity Patients with PNH should be given trans fusions only with red cells from which the plasma has been *separated the cells having been repeatedly washed in saline* No other measures have proved effective in avoiding crises which are also provoked by a great variety of stimuli Many chemicals including drugs given parenterally and orally in fections physical injury fatigue and anxiety have been asso ciated with crises

Anemia in PNH is hemolytic due to a short red cell life and a relative deficiency of hemoglobin synthesis It may be disproportional to the degree of hemolysis depending on these two factors The marrow is usually hyperplastic but extramedullary hemopoiesis is uncommon Sometimes for no apparent reason hemopoiesis ceases abruptly with consequent

severe anemia and agranulocytosis but purpura is rare

Leukocyte counts are usually less than 5 000/cu mm and in infections or crises they do not reach expected levels Platelet counts are often about 100 000/cu mm but may be normal As with the lowest leukocyte counts the lowest platelet counts are recorded in patients with very severe anemias Leukopenia or thrombocytopenia does not seem to be due to impaired formation nor does any hypersplenic phenomenon operate so that there must be abnormally rapid elimination of the cells elsewhere In vitro experiments support the view that leukocytes and platelets are abnormally susceptible to injury Thus PNH is probably due to a defect of the red cells leukocytes and platelets possibly an abnormality of stromal protein which renders them susceptible to the proteolytic activity of the PNH hemolytic system

Dicumarol* inhibits PNH hemolysis but is ineffective in hemolytic crises and does not consistently relieve the anemia It is however of value in patients with painful venous thromboses as it relieves pain and sometimes allows the red cell count to rise Heparin in high concentrations inhibits hemolysis but in the dilutions obtaining in the patient it actually augments it ACTH and cortisone are ineffective Epinephrine may cause abrupt cessation of hemolysis but the effect is short lived and is followed by hemoglobinuria As this drug increases blood coagulability its use is contraindicated

Heredity age sex race and endocrine dysfunction play no part in PNH Nutritional deficiency has not been excluded In some ways the condition resembles pernicious anemia but vitamin B_1 therapy has never been successful The long survival time of many patients excludes a neoplastic disease Infection may be important Possibly the disease represents a perverted immune response producing abnormal stromal protein instead of abnormal protein globulin (antibodies)

[This article is an extensive summary and contains excellent illustrations and a large bibliography —Ed]

PERNICIOUS AND OTHER NUTRITIONAL MACROCYTIC ANEMIAS

Characteristic Cellular Changes in Epithelial Cells in Pernicious Anemia Although blood cells have been extensively studied in pernicious anemia little attention has been ... to

other cells despite the clinical evidence of oral epithelial changes presented by the occurrence of glossitis During routine cytologic studies of sputum and gastric juice for cancer cells Ruth M Graham and Maud H Rheault[1] (Massachusetts Gen l Hosp) noted specific cellular changes in patients with pernicious anemia These changes were thought to merit further study

Studies were made on 41 patients with pernicious anemia Twenty were in relapse and of these 15 were being studied



F g 54 (l ft) —Normal pe fi ial q m s ll
F g 55 (gbt) —Tb ee p th lial cell w th la g n l bow g abnormal h om t n gem t
(Court y f G h m R M d Rhea lt, M. H J Lab & Cl n, Med 43 235 245 F b y 1954)

for the first time the others were in therapeutic remission All had severe macrocytic anemia before treatment and responded to liver or vitamin B_1 therapy All had histamine fast achlorhydria Hemoglobin values of patients in relapse were with one exception below 8 5 Gm /100 cc Values for patients in remission were above 12 5 Gm

Method—Patients fast after 7 p m the previous evening and all secretion in the fasting stomach is removed through a multiple holed stomach tube This is specimen 1 Saline 100 ml is introduced into the stomach and allowed to remain 15 minutes during which the patient turns from side to side several times As much as possible of this solution is withdrawn and is specimen 2 Because epithelial cells deteriorate rapidly the specimens are immediately

(1) J Lab & Cl Med 43 235 245 F b y 1954

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Characteristic Cellular Changes in Epithelial Cells in Pernicious Anemia. Although blood cells have been extensively studied in pernicious anemia little attention has been paid to

Observations on Etiologic Relationship of Achylia Gastrica to Pernicious Anemia XV Hemopoietic Effects of Simultaneous Intravenous and of Simultaneous or Serial Oral Administration of Intrinsic Factor and Vitamin B_1 Ralph O Wallerstein John W Harris Robert F Schilling and William B Castle[2] (Harvard Med School) studied 15 patients with relapsed or untreated pernicious anemia (diagnosed on the basis of typical blood and marrow morphology and histamine fast achlorhydria) given normal human gastric juice and vitamin B_{12} in various doses and combinations orally and parenterally Dietary conditions were controlled Reticulocytes were estimated daily and red cells hemoglobin and hematocrit every third day

Vitamin B_1 was separately incubated with inactivated and uninactivated gastric juice and the hemopoietic activity of the mixtures assayed by observing the reticulocyte response in patients to whom they were given intravenously No evidence was obtained that intrinsic factor enhances the potency of vitamin B_1 given parenterally

The patients responses also showed that in simultaneous daily oral administration of vitamin B_1 and intrinsic factor an increase in the amount of either material enhanced the hemopoietic effect but parenteral vitamin B_{12} alone was even more effective Further the effect of vitamin B_1 was detectably more enhanced when oral administration of gastric juice preceded by a few hours that of vitamin B_{12} than when this order was reversed

The view that intrinsic factor acts on vitamin B_{12} to produce a more active hemopoietic complex received little support from these observations

Possibly the function of intrinsic factor is to promote absorption probably in the upper intestine of vitamin B_1 This view is supported by the recent discovery that intrinsic factor can produce in pernicious anemia patients receiving radioactive cobalt containing vitamin B_1 a decrease in the fecal excretion of radioactive material and also by the fact established here that in the serial oral administration of gastric juice and vitamin B_1 the hemopoietic effect is greater when the intrinsic factor is given before the vitamin B_1 Consistent also is the lack of potentiation of vitamin B_1 by intrinsic factor on simultaneous cutaneous injection

(2) J Lab & Cl M d 41 363 375 M b 1953

centrifuged and sediment from each is placed on two marked slides The four slides are fixed in equal parts of alcohol and ether for at least 30 minutes and then stained by Papanicolaou s technic

In untreated patients with pernicious anemia the superficial squamous cells showed marked changes the most prominent being an increase in size of both cytoplasm and nucleus On an average these cells were 16 μ larger in their greatest diameter than those from normal patients (Fig 54) or from pernicious anemia patients in remission Multinucleation and clumping of the nuclear chromatin (Fig 55) were also observed Columnar cells showed similar changes with increase in size multiple nuclei and increased clumped nuclear chromatin After liver or vitamin B_1 therapy these changes in both types of cells decreased greatly and were almost absent in patients in remission Price Jones curves on secretions from 15 untreated patients and on 10 normal subjects quantitatively confirmed these observations Phagocytic histiocytes from sputum are often seen in gastric smears These cells were also increased in size in untreated pernicious anemia

To assess the effect of therapy on the other cellular changes gastric epithelial cells were counted as abnormal if they showed increased size multiple nuclei or bizarre chromatin arrangement Patients with pernicious anemia had 14 53% abnormal cells (average 28%) and patients in remission had an average of 8% abnormal cells three having more than 15% the abnormality in all being increase in size Gastric smears from four patients with severe iron deficiency anemia and three with acute blood loss showed no such abnormalities

These cellular abnormalities are not apparently due to a low hemoglobin as they were not seen in the anemic controls Also histamine fast achlorhydria is probably not significant as patients in remission still had achlorhydria Evidence points to the lack of extrinsic factor (vitamin B_1) as the cause of the changes Abnormal cellular forms have also been noted in sputum and in oral and vaginal smears and together with abnormalities of red cells white cells epithelial cells and histiocytes would indicate that the same factor in all cases is required for normal maturation

[A contribution of profound biologic interest. In pernicious anemia macrocytosis and other morphologic evidences of defective nucleoprotein synthesis are thus shown to characterize many cell systems —Ed]

vitamin B_{12} absorption shown by the increase in surface radioactivity detected over the liver (Glass) or in the urine after a "flushing" parenteral dose of nonradioactive vitamin B_{12} (Schilling) as described in the next article.—Ed.]

Effect of Gastric Juice on Urinary Excretion of Radioactivity after Oral Administration of Radioactive Vitamin B_{12} was studied by Robert F Schilling[4] (Univ of Wisconsin) Heinle and his associates have reported that the simultaneous oral administration of an intrinsic factor preparation and 0.5 µg radioactive-cobalt-containing vitamin B_{12} by mouth *reduces* fecal radioactivity resulting from the oral administration of radioactive vitamin B_{12} alone in pernicious anemia. Taken with other evidence, this suggests that the function of *intrinsic factor is to promote the absorption of vitamin B_{12}* from the intestinal tract. The author presents positive evidence in support of this hypothesis by showing that the quantity of radioactivity in the urine of pernicious anemia patients is *increased* by intrinsic factor administration when the patient is given a subcutaneous "flushing" dose of 1 mg nonradioactive vitamin B_{12}.

TECHNIC.—Normal subjects or pernicious anemia patients in complete remission after therapy were studied. A single sample of vitamin B_{12} containing radioactive cobalt (Co^{60}) with a specific activity of 245 µc./mg was used as the source of tracer vitamin. After voiding fasting subjects were given 2 µg radioactive-cobalt containing vitamin B_{12} by mouth at 8.30 a.m. and two hours later a subcutaneous injection of 1 mg nonradioactive vitamin B_{12}. Urine secreted during the next 24 hours was saved. Urine radioactivity was determined by evaporating 2 ml. samples to dryness in a cup-type pan and counting in a windowless flow counter. When duplicate samples were not in good agreement two more were dried and counted. Normal human gastric juice collected after histamine stimulation was neutralized and passed through a Berkfeldt filter.

Under these conditions six normal subjects excreted definite amounts of radioactivity in the urine but six patients with pernicious anemia excreted none except when given simultaneously with the tracer dose of radioactive vitamin B_{12}, normal human gastric juice containing active intrinsic factor. When in one patient active gastric juice was given 12 hours after a tracer dose of radioactive vitamin B_{12} no radioactivity appeared in the urine. The oral administration of oxytetracycline for the purpose of sterilizing the upper alimentary tract did not result in the appearance of radio[illegible] in the

(4) J Lab & Clin. Med 42 860-866 December 1953.

Concentration of Intrinsic Factor and Vitamin B_1 Binding Activities of Fractions of Desiccated Hog Stomach W H Prusoff A D Welch R W Heinle and G C Meacham[1] (Western Reserve Univ) made extracts in 2% sodium chloride of desiccated hog stomach of proved therapeutic value in pernicious anemia These were fractionated by precipitation with ammonium sulfate at 35 and 55% and full saturation The protein content of each fraction was determined and they were then separately assayed for intrinsic factor activity by observing the therapeutic response in pernicious anemia patients in relapse of that amount of fraction corresponding to 50 Gm dried stomach and 5 μg vitamin B_1 given daily These patients had previously been tested for therapeutic response to this dose of vitamin B_1 for 10 days failing a response during the combined assay the patient s ability to respond was tested by known materials subsequently

Fraction B obtained at 55% saturation with ammonium salt contained the least protein and the greatest intrinsic factor activity no localization of which was observed in further fractions separated by dialysis Electrophoretically fraction B was found to be heterogeneous with at least seven components

The ability of the fractions to bind vitamin B_1 was assessed by their capacity to prevent growth of Lactobacillus leichmannii in the presence of the vitamin The capacity of fraction B was intermediate between those of the other fractions This relation between the various binding capacities was confirmed by dialysis of the fractions after mixture with vitamin B_1

Thus the fraction with most intrinsic factor activity had less binding potential than another fraction with less clinical activity In absence of correlation the binding capacity cannot be used as an effective guide to the isolation of intrinsic factor from gastric tissue The true relationship between intrinsic activity and vitamin B_1 binding power must await further purification of the factor and more reliable methods of assay A new assay technic in which the intake of intrinsic factor decreases the excretion of radioactivity in pernicious anemia patients given minute doses of cyancobalamin Co^{60} is promising [And has now been confirmed by other observers with variations in the method of detection or measurement of the

(1) Blood 8 491 501 J e 1953

folinic acid or intrinsic factor alone In 11 of 14 cultures vitamin B_{12} plus intrinsic factor showed less maturing effect than vitamin B_1 alone and never showed more Clearcut results are difficult to obtain with this technic and only a few of the observed variations were statistically significant but this observed trend is almost certainly valid The claim that intrinsic factor enhances the maturing effect of vitamin B_1 could not be substantiated and it appears that intrinsic factor makes vitamin B_1 less available for use by red cells growing in vitro

↓ The following two articles indicate much progress toward and perhaps even final success in the identification of the so called intrinsic factor of gastric juice The mucinous characteristics and the somewhat different properties of the purest preparations isolated by different workers render it difficult to know whether or not this active principle has been isolated or only a carrier mucoprotein —Ed

Oral Treatment of Pernicious Anemia with Small Doses of Vitamin B_1 Combined with Mucinous Materials Derived from Hog Stomach George B Jerzy Glass and Linn J Boyd[6] (New York City) treated 20 patients with pernicious anemia under controlled dietary conditions and close hematologic observation with small oral doses of vitamin B_1 in combination with intrinsic factor containing mucinous materials obtained from hog stomach The sources of intrinsic factor used were commercial gastric mucin acetic acid extracts of hog pyloric mucosa mucinous materials precipitated by acetone or by saturation with ammonium sulfate from hydrochloric acid extracts of hog pyloric mucosa mucous fractions obtained from further fractionation (electroconvection) of ammonium sulfate precipitates and a commercial preparation in which intrinsic factor concentrate is combined with small amounts of vitamin B_1

Results indicated that mucous substances extracted from hog pyloric mucosa exhibit intrinsic factor activity when given orally with small doses of vitamin B_{12} to pernicious anemia patients The intensity of this effect depends on the method of preparation of the material acetone precipitation for example causing some loss of intrinsic factor potency It also depends on the dose of the material the responsiveness of the patient and the quantity of vitamin B_1 given jointly Various materials similarly processed failed to produce con

(6) Blood 8 867 89 Oct be 1953

urine until the patient was given active gastric juice simultaneously with the tracer vitamin Unless the flushing injection of nonradioactive vitamin B_1 was given no radioactivity was detected in the urine of normal persons or of *pernicious anemia patients under any of the above circumstances* Plasma samples showed no radioactivity

Extraction with N butanol of normal urine to which had been added radioactive vitamin B_{12} like extraction of patient s urine containing similar amounts of excreted radioactivity showed approximately 60% recovery This suggests as does the flushing effect of nonradioactive vitamin B_{12} that the radioactivity in the urine was in the form of radioactive vitamin B_1 In patients with pernicious anemia intrinsic factor is lacking according to both earlier studies of hemopoietic responses and the present observations

[Contradictory observations in pernicious anemia admittedly conducted with difficult technics favor either (*a*) a direct maturing action of vitamin B_{12} on bone marrow megaloblasts in vivo (Horrigan) or (*b*) an indirect maturing action requiring at least in vitro an additional substance present in both gastric juice and normal serum (Lajtha) *That* the intrinsic factor of gastric juice in vivo promotes the intestinal absorption of vitamin B_{12} (Schilling) and does not enhance its parenteral effectiveness (Wallerstein) at least favor the simpler hypothesis (*a*) as does the next article —Ed]

Effect of Vitamin B_1 and Intrinsic Factor on Maturation of Megaloblasts in Tissue Culture is described by Edward H Reisner Jr and Harold T Swan[5] (Cleveland) Marrow from pernicious anemia patients in relapse grows readily in tissue culture Growth is poor in serum from pernicious anemia patients but when vitamin B_1 is added growth becomes vigorous with increased hemoglobinated erythroblasts

By Lajtha s modified Osgood technic 10 megaloblastic marrows from pernicious anemia patients were cultured in mediums consisting of pernicious anemia serum plus various combinations of *vitamin B_1 gastric juice intrinsic factor* and folinic or folic acid The percentages of megaloblasts and normoblasts were compared with a control Four megaloblastic marrows from two patients one with sprue and the other with a megaloblastic hemolytic anemia both of whom had responded to vitamin B_{12} were similarly cultured

Maturation occurred in all controls at variable speeds and was inconstantly affected by the addition of vitamin B_1

(5) Proc Cent I Soc Cl R 6 80 1953

salt solutions and at various pH values the authors isolated active mucoprotein without preparative electrophoresis Most of the activity can be extracted by use of a suitable buffer solution at pH 6 35 and the final fraction is easily soluble at *pH 2 0* Chemical analyses of the new material and of that obtained by electrophoresis show a close similarity and by observing the effect of the new material on fecal excretion of oral radioactive vitamin B_1 it appears to be 15 times more active than fraction B obtained by ammonium sulfate precipitation of hog stomach mucosal extract

Paper electrophoresis indicates that these materials are essentially homogeneous Ultracentrifuge studies of the new material show that it contains a small amount of protein of high molecular weight which sediments rapidly The remainder 95% of the original appears homogeneous and has a molecular weight below 20 000

[In the *Lancet* for May 29 1954 the authors reply to detailed criticism by G B Jerzy Glass of the paper presented here Dr Glass s letter appears in the *Lancet* for May 2? Latner and his associates state that their material is now homogeneous during electrophoresis at different pH levels and ionic strengths and in the ultracentrifuge The claim is made that their preparation possesses clinical activity some hundred times greater than soluble glandular mucoprotein as identified by Glass from among the number of different mucoproteins present in gastric juice Further chemical details and data concerning clinical trials are to be published as soon as possible—Ed.]

Serum Vitamin B_1 Concentrations of Patients with Megaloblastic Anemia after Treatment with Vitamin B_1 Folic Acid or Folinic Acid were studied by D L Mollin and G I M Ross[8] (Postgrad Med School of London) Vitamin B_1 concentrations in the serum and urine of normal subjects untreated pernicious anemia patients and pernicious anemia patients during the first 72 hours of vitamin B_1 therapy have previously been reported In the present study serial bone marrow examinations were made after single intramuscular injections of the vitamin in 33 patients with pernicious anemia *in relapse* or who had received no treatment for six months Strict dietary control was exercised throughout and serum vitamin assays were made frequently usually daily using Euglena gracilis var bacillaris as test organism

In pernicious anemia patients serum vitamin B_1 concentrations rose from low pretreatment levels to within normal range after single injections of 20 1 000 μg vitamin B_1 and

(8) B r M J 2 640 645 S pt 19 1953

sistent results Compared with glandular mucoprotein of human gastric juice also used as a source of intrinsic factor materials of animal origin appear to be a heterogeneous com plex of various mucous substances

Responses obtained with a commercial preparation indi cated that a daily dose of 15 μg vitamin B_{12} combined with not more than 50 mg intrinsic factor concentrate is roughly equivalent to a USP unit of an oral antianemia preparation The response to massive weekly dosage was even better when for example 150 μg vitamin B_{12} and 250 mg intrinsic factor concentrate were given This is probably the treatment of choice in pernicious anemia when rapid improvement is de sired Studies on two patients with pernicious anemia indicate that the commercial preparation is thermostable its hemopoi etic activity being preserved after it was boiled in water for 30 45 minutes Since intrinsic factor is thermolabile it is possible that the intrinsic factor of hog stomach becomes thermostable after the interaction in vitro with vitamin B_{12} or that the hemopoietically effective product of this binding is thermostable under the conditions which obtained

Isolation of Castle's Intrinsic Factor Previous attempts to isolate this substance have not met with much success but A L Latner R J Merrills and Laureen C D P Raine[7] believe that they have isolated it in a satisfactorily pure state and that it is mucoprotein in nature

Concentrates of intrinsic factor from human gastric juice have been obtained by a preparative paper strip electropho resis technic The concentrates remained in solution in a buffer at pH 6 35 and were tested for potency on pernicious anemia patients Subsequently this technic was applied to concen trates from hog gastric mucosa The buffer electrolytes were removed by ultrafiltration and the solutions freeze dried The highly active solid material so obtained was mucoprotein in nature and was not soluble glandular protein This material was tested for intrinsic factor activity by determining its effect on fecal excretion of orally administered radioactive vitamin B_1 A diminished excretion was taken as evidence of such activity

By making use of data obtained from a study of the varia tion in the solubility of the electrophoresis material in certain

(7) Lancet 1 497 498 M r 6 1954

logic responses were less different both marrows being normoblastic on the 7th day The initial red cell improvement was greater after the larger dosage but by the 15th day both rates of increase were the same

A dosage of 40 μg vitamin B_{12} every 10 days or 160 μg every 21 days maintained the serum vitamin B_{12} levels of most pernicious anemia patients at normal values and would *seem to be the minimal desirable dosage* The tissue reserves of vitamin B_1 estimated at about 1 000 2 000 μg are seriously depleted in pernicious anemia patients yet a single small dose has a noticeable effect on the vitamin B_1 serum concentration This suggests that the tissue reserve becomes depleted to maintain a normal serum concentration Thus much larger initial doses of the vitamin (up to 5 mg) are probably to be recommended during the first week to replenish the depleted tissue reserve the better subsequently to maintain normal serum concentrations

In megaloblastic anemias due to vitamin B_1 deficiency the serum concentration of the vitamin was not affected by folic or folinic acid therapy The vitamin B_1 serum concentrations of 12 patients with megaloblastic anemia associated with sprue or pregnancy were normal before treatment and unaffected by vitamin B_{12} therapy which was ineffective hematologically Folic or folinic acid to which the patients responded also did not alter the serum vitamin B_1 levels

[A practical therapeutic point derives from the observation that most of the vitamin B_{1} when given in a single injection of more than 30 μg is promptly excreted in the urine —Ed.]

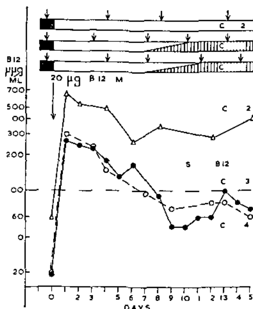
Studies of Vitamin B_1 in Serum and Urine Following Oral and Parenteral Administration are reported by Walter G Unglaub Harold L Rosenthal and Grace A Goldsmith[9] (Tulane Univ) To provide more information about the absorption utilization and excretion of vitamin B_1 microbiologic assay technics were used to analyze serum and urine from normal subjects and patients with megaloblastic anemia before and after parenteral and oral administration of the vitamin

PROCEDURE —At first subjects were given a restricted diet but later studies showed the suspected food had no significant effect on vitamin activity of serum or urine Therefore diets in the latter part of the study were not o restricted In all subjects blood counts were either stable or falling at the time of the test. Subjects fasted

(9) J Lab & Cl M d 43 143 156 J ry 1954

remained there from 6 to more than 18 days after a dose of 20 μg and 34 58 days after 1 000 μg with periods of proportional length after doses of 40 80 160 and 320 μg The mean of the concentrations of all patients in each treatment group fell in a few days below the mean concentrations found in normal subjects

In untreated pernicious anemia patients in whom the vitamin B_{12} serum concentration rose to normal after an injection of the vitamin the marrow became normoblastic but megaloblasts reappeared a few days after the serum vitamin B_1 concentration fell below 100 μμg/ml the low limit of normal At levels above this the marrows remained normoblastic (Fig 56)



F g 56 —S rum tam n B_{12} n nt at nd b n m ow hang s afte intramu l ject ns of 20 μg v t m n B_{12} i thre p t ts w th pe ou a m a Bla k p e ts m galobl t b m po es rt cally l ned ar i t r med t m g lobl t b m po d p n ar , orm bl t h mopo A ow nd t t mes of m ow b p y (C u t y of Moll n D L nd Ros G I M B t M J 2 640 645 Sept. 19 1953)

Compared with the effects of a daily dose of 40 μg vitamin B_1 a daily dose of 1 μg did not maintain the serum vitamin B_1 concentration at consistently normal levels The hemato

serum vitamin B_1 activity and urinary excretion of the vitamin was apparent Maximum levels of total serum activity and urinary excretion tended to increase with repeated oral doses of the vitamin No correlation was observed between maximum total serum vitamin B_{12} activity and hemopoietic response

Alteration of Ascorbic Acid Oxidation in Pernicious Anemia John J Will John F Mueller Helen S Glazer Ben I Friedman and Richard W Vilter[1] (Cincinnati) state that although the relation of ascorbic acid and its oxidation product dehydroascorbic acid to erythropoiesis is not established ascorbic acid seems essential for conversion of folic to folinic acid Vitamin C deficiency is important in the etiology of megaloblastic anemia of infancy and in pernicious anemia minor hematologic responses may follow large doses of ascorbic acid Abnormally low vitamin C levels have been found in the plasma and leukocytes of pernicious anemia patients with adequate intakes of vitamin C This suggests that in pernicious anemia there might be excessive oxidative destruction or utilization of ascorbic acid To test this hypothesis ascorbic and dehydroascorbic acid levels were determined in seven pernicious anemia patients in severe relapse and in five controls Blood was taken before 300 mg sodium ascorbate was administered intravenously and at 15 minutes and 1 2 and 3 hours afterward

The 15 minute plasma specimens of the controls showed a prompt rise of ascorbic acid and a lesser rise of dehydroascorbic acid with a fall in both levels in the later samples approaching predosage levels

Of the seven pernicious anemia patients in relapse two showed similar levels to the controls but in the other five there was a striking difference The 15 minute samples of these five showed a prompt rise of dehydroascorbic acid and little or no rise of ascorbic acid At one two and three hours there was a fall in dehydroascorbic acid levels approaching predosage values but no rise in ascorbic acid After specific antianemic treatment normal responses to the injection of ascorbic acid were established

Oral Treatment of Pernicious Anemia with Citrovorum Factor (Leucovorin) Arthur Sawitsky Leo M Meyer Robert

(1) P oc. C t 1 S Ch R 6 113 1953

for eight hours before a sample of blood was taken and the dose of vitamin B_{12} given Blood was again removed 1 4 8 and 24 hours thereafter food was withheld until after the four hour sample was taken Serum was separated and stored frozen until analysis Urine was collected for 24 hours with glacial acetic acid as preservative Aliquots were adjusted to pH 6 8 and stored frozen Microbiologic assay of vitamin activity was made by standard technics using Lactobacillus leichmannii Values obtained were not corrected for the presence of nonspecific activity

Before the vitamin was given serum vitamin activity of six patients with pernicious anemia in relapse and two with nutritional macrocytic anemia was significantly less than in normal subjects and patients with polycythemia vera second ary polycythemia and iron deficiency anemia Urine vitamin activity in patients with pernicious anemia did not differ sig nificantly from that in the normal subjects

Following injection of 10 100 μg vitamin into eight nor mal subjects and 25 μg into two pernicious anemia patients there was at one hour a prompt rise of serum vitamin activity which decreased rapidly for three hours after and then more slowly for the rest of a 24 hour period Serum vitamin activity of the anemic patients did not differ significantly from that of normal subjects despite the low preinjection levels of the former In all subjects serum activity was greater at 24 hours than before injection Urine vitamin activity increased roughly in proportion to the dose of vitamin given Increase was slightly less in two anemic patients than in normal sub jects and hematologic response was suboptimal

Oral administration of vitamin B_1 to normal subjects was followed by little or no change in serum activity after 500 μg slight increase after 1 000 μg and a definite rise after 3 000 μg In two patients with relapsed macrocytic anemia oral ad ministration of vitamin B_1 was followed by a slight increase of serum activity to within normal limits after 500 μg and a definite increase in one patient after 1 000 μg After 3 000 μg a moderate to marked rise in serum activity was seen in five of six patients The hemopoietic response was suboptimal in all patients given less than 3 000 μg

Urine vitamin B_{12} activity following oral doses of 500 or 1 000 μg differed little from predosage levels After 3 000 μg an increase in urine vitamin B_{12} activity equivalent to that which followed intramuscular injection of 10 μg was noted in most instances No definite relation between maximum total

serum vitamin B_{12} activity and urinary excretion of the vitamin was apparent Maximum levels of total serum activity and urinary excretion tended to increase with repeated oral doses of the vitamin No correlation was observed between maximum total serum vitamin B_1 activity and hemopoietic response

Alteration of Ascorbic Acid Oxidation in Pernicious Anemia John J Will John F Mueller Helen S Glazer Ben I Friedman and Richard W Vilter[1] (Cincinnati) state that although the relation of ascorbic acid and its oxidation product dehydroascorbic acid to erythropoiesis is not established ascorbic acid seems essential for conversion of folic to folinic acid Vitamin C deficiency is important in the etiology of megaloblastic anemia of infancy and in pernicious anemia minor hematologic responses may follow large doses of ascorbic acid Abnormally low vitamin C levels have been found in the plasma and leukocytes of pernicious anemia patients with adequate intakes of vitamin C This suggests that in pernicious anemia there might be excessive oxidative destruction or utilization of ascorbic acid To test this hypothesis ascorbic and dehydroascorbic acid levels were determined in seven pernicious anemia patients in severe relapse and in five controls Blood was taken before 300 mg sodium ascorbate was administered intravenously and at 15 minutes and 1 2 and 3 hours afterward

The 15 minute plasma specimens of the controls showed a prompt rise of ascorbic acid and a lesser rise of dehydroascorbic acid with a fall in both levels in the later samples approaching predosage levels

Of the seven pernicious anemia patients in relapse two showed similar levels to the controls but in the other five there was a striking difference The 15 minute samples of these five showed a prompt rise of dehydroascorbic acid and little or no rise of ascorbic acid At one two and three hours there was a fall in dehydroascorbic acid levels approaching predosage values but no rise in ascorbic acid After specific antianemic treatment normal responses to the injection of ascorbic acid were established

Oral Treatment of Pernicious Anemia with Citrovorum Factor (Leucovorin) Arthur Sawitsky Leo M Meyer Robert

(1) P c C t l Soc Cl n R 26 113 1953

anemias The hemopoietic effect of chlortetracycline has been attributed to an increase in citrovorum factor production in duced *by the antibiotic either by destroying antagonizing or* by promoting synthesizing bacteria In animals it has pre vented the inhibitory effect of folic acid antagonists and in others hematologic changes have responded to both chlortetra cycline and folic acid but not to liver or vitamin B_{12} Both of the authors patients responded well to purified liver extracts containing no folic acid and neurologic changes were present that are not favorably influenced by folic acid On the other hand neurologic changes have cleared up in the course of *treatment with citrovorum factor*

[In addition to the explanations offered by the authors there remain the possibilities of responses (*a*) specifically to vitamin B_{12} present as a contaminant in the antibiotics or (*b*) nonspecifically to the abolition of a source of toxic products of bacterial metabolism The former is chiefly suggested by the reported (though undocumented) hemopoietic responses to purified liver extract and the presence of neural lesions in each patient Of course even with vitamin B_{12} deficiency the demonstrated hemopoietic responses to the antibiotics could have been the result of more available folic acid or citrovorum factor for absorption—Ed]

Treatment of Megaloblastic Anemias Relation of Penicil lin to Vitamin B_1 Henry Foy and Athena Kondi[4] after having found that the response of megaloblastic anemias in Africans *to penicillin closely resembles that obtained* in similar anemias by potent hematinics further found that the anemias which do not respond to penicillin also do not respond to vita min B_{12} given orally

The patients studied had severe anemia with red cell counts of 500 000 2 500 000/cu mm megaloblastic bone marrow and mean corpuscular volumes between 80 and 140 cu μ Most of them had elevated serum bilirubin (indirect) values and a positive reaction to the plasma hematin test These anemias were known to respond to crude liver or folic acid and often to orally or intramuscularly administered vitamin B_{12} Some patients had histamine fast achlorhydria a few of these showed on gastroscopy gastric atrophy and must therefore be regarded as having true pernicious anemia although no nerve involvement or glossitis was present

On the basis of therapeutic responses there are in Afri cans three types of megaloblastic anemia Type 1 responds to penicillin *and all known hematinics Type 2 does not respond* to penicillin or orally administered vitamin B_1 but does re

(4) Lancet 2 1280 1285 Dec 19 1953

spond to the vitamin intramuscularly Type 3 responds only to folic acid Clinically and hematologically there was no difference in the types So far 24 patients with megaloblastic anemia have been treated with penicillin 16 of whom had typical specific responses 4 did not respond either to penicillin or

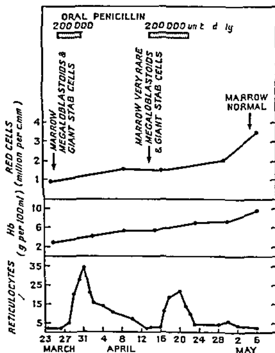


Fig 57—Typ 1 m Doubl p s t p ll n g v lly (Court sy f F y H d Ko d A La t 2 1 80 1285 D c. 19 1953)

to vitamin B_{12} orally but did respond to the vitamin given intramuscularly and 4 responded only to folic acid

Woman 24 had splenomegaly and slight ankle edema in the last month of pregnancy Blood examination showed 845 000 red cells/cu mm 2 8 Gm /100 ml hemoglobin mean corpuscular volume of 118 cu μ and mean corpuscular hemoglobin concentration of 28% The marrow was megaloblastic and the reaction to the histamine test meal normal Serum bilirubin level was 3 mg /100 ml there was no sickling and malarial parasites were not seen She was observed for three day during which the reticulocyte count remained

below 0 7% (Fig 57) She was then given 200 000 units of penicillin orally per day for six days when the reticulocyte count reached 32% In the next 11 days it fell to 1% Penicillin was again given in the same doses for nine days On the seventh day the reticulocyte count was 20% Two weeks later she left the hospital with a red cell count of 2 900 000 9 Gm hemoglobin and normal bone marrow

The response of type 1 anemias to penicillin and the failure of type 3 to respond to penicillin but subsequently to folic acid suggest that penicillin affects synthesis metabolism or absorption of vitamin B_1 but not of folic acid In one case of type 2 anemia early relapses responded to penicillin and orally administered vitamin B_{12} but with development of complete achlorhydria vitamin B_{12} had to be given intramuscularly Thus penicillin like oral vitamin B_1 is inactive unless intrinsic factor be present

The response to penicillin is probably based on changes produced in the intestinal flora Antibiotics can accelerate animal growth and injected penicillin being excreted into the gut in bile is as effective as penicillin orally The response of the anemia is similar to that obtained by established hematinics which are held not to suppress infection but rather to supply some hemopoietic deficiency In the chick intestinal flora may retard growth sterile chicks growing better than nonsterile ones and those given antibiotics growing best of all

Dietary variations may alter the intestinal flora and the prevalence of megaloblastic anemia in primitive communities may be related to a diet rich in bulky carbohydrate and poor in first class protein thus encouraging a flora inimical to production of essential metabolites

Studies with Inagglutinable Erythrocyte Counts VI Accelerated Destruction of Normal Adult Erythrocytes in Pernicious Anemia, Contribution of Hemolysis to Oligocythemia The importance of hemolysis in pernicious anemia has been minimized by the normal survival of normal red cells in the circulation of patients together with the curative effect of vitamin B_{12} To establish the presence of a hemolytic mechanism in the disease and to assess the effect on it of vitamin B_{12} therapy Henry E Hamilton Elmer L DeGowin Raymond F Sheets Clinton D Janney and Jason A Ellis[5] (State Univ of Iowa) carried out differential agglutination studies

(5) J Cl I st 33 191 05 F bru ry 1954

on pernicious anemia patients in relapse or under treatment who were of blood group A or B and had been transfused with normal group O red cells

METHOD —Normal blood was collected in sodium citrate solution and stored for less than 18 hours at about 4 C Plasma was separated and the red cells were washed once in saline the original volume being then restored with saline After a red cell count on the recipient the red cells from 500 ml blood were transfused Subsequently simultaneous differential and total red cell counts were made

Red cells from an untreated pernicious anemia patient were destroyed at random in the circulation of the normal

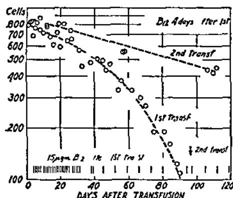


Fig 58—R d m l f f h m l yth o vt t f s d t p t t w th pe m t t d w th vit m n B_{12} S m l g thm cal op n ci les v l l l t d f m b d ggl t bl ll ou t t mp sat f r ll lost by mal g g Eryth yt ñ t t f n w j t d f d y b f v tam B_{12} ther py w b gu d we l t t d m w th t l t g c ll b cam ld D g fi t 40 d ys f tudy t f d m l w b t 0 9% d f om 60 t 90 d y bout 3 3% S d t f f m m dono w g n 97 d y ft fi t d d s ll h b t d on t t d m lo f b t 0 4% th h w g th t d tru t v m h m n p ti t h d t b m pl t ly b l h d by v t m n B_{12} t tm t f t l st 97 d y (C t y f H m l to H E J Cl I t 33 191 05 F bru ry 1954)

subject at the same rate as normal cells transfused to the patient In eight untreated patients red cells were destroyed at random irrespective of the age of the cells The action of the hemolytic mechanism responsible was blocked by giving 15 μg vitamin B_1 daily for nine but not for three days before transfusion Once they were exposed to the vitamin B_1 deficient milieu even for a few hours the normal red cells were damaged and subsequent therapy did not reverse the effect (Fig 58) However after adequate therapy retrans

fusion of two patients with blood from the same donors was followed by decreased random loss (Fig 58) and was actually zero in one This excludes antisensitization to donor s cells as a cause of hemolysis In one patient 15 μg vitamin B_1 daily for 23 days protected transfused cells from random destruction for only 20 days after cessation of therapy These findings suggest that deficiency of vitamin B_{12} exerts a noxious influence on normal red cells in the circulation In four of six untreated patients oligocythemia could be entirely accounted for by this random destruction as measured by loss of normal transfused red cells In two other patients maturation arrest was an additional factor

Five of six patients responded to vitamin B_{12} therapy by acceleration of the rate of erythrocyte release to the circulation to twice the normal rate whereas the single patient with an initial red cell count of 3 500 000/cu mm showed a normal rate during treatment During the untreated state vitamin B_{12} *deficiency seems to inhibit acceleration of the rate of* erythrocyte release above normal in response to oligocythemia This is in contrast to other types of hemolytic anemia [without additional decreased red cell production —Ed]

[In view of the impression of prompt and striking clinical benefit from even a single injection of vitamin B_{12} it seems remarkable that there is such delay in the abolition of the hemolytic process after repeated injections and that this process may remain in abeyance only 20 days after cessation of therapy —Ed]

Anemia of Adult Scurvy In a study of 32 patients African Negro men aged 22-60 B Bronte Stewart[6] (Univ of Cape Town) attempted to assess the importance of vitamin C as an erythropoietic factor Scurvy had developed when they were on a diet completely lacking in vitamin C Thirteen men who were studied intensively continued on this diet in the hospital and remained in bed After a control period of varying length ascorbic acid in 1 000 mg doses was given intravenously every day but the full hospital diet was not allowed until the hematocrit value rose above 40 ml /100 cc The other 19 patients received ascorbic acid and full hospital diet immediately on admission

Anemia is common in scurvy 80% of these patients having hematocrit values below 40 ml /100 cc In most it was severe the lowest value recorded being 8 ml /100 cc Patients not anemic showed only mild scorbutic symptoms The anemia

(6) Q rt J Med 22 309 329 J ly 1953

was usually normocytic and normochromic In four of the severe cases it was macrocytic but in only one the most severe was the bone marrow megaloblastic Anisocytosis was most marked in severe cases but poikilocyto is was rare In five cases the initial reticulocyte count was raised and in some severe cases in which there had been a long control period of rest the reticulocytes increased irrespective of the initial levels White cell counts were normal or low Platelet counts and bleeding coagulation and prothrombin times were

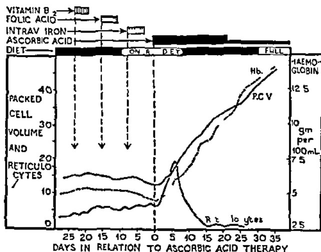


Fig 59—Effect f tam n B_{12}, f l d n t sly d ynth t scorb c d n f s urvy w th a m (C rt y of B t Stew rt B Q t J M d 2 309 329 July 1953)

normal in all cases studied Bone marrows were hypercellular The degree of hypercellularity increased with the severity of the anemia but mitosis decreased Gastric analyses of 12 patients revealed histamine fast achlorhydria in 7 and hypo chlorhydria in 3 Low plasma iron and iron binding capacities were noted in association with hematomas Extravascular hemolysis in these hematomas caused increased pigment ex cretion

In all cases rest in bed was followed by improvement with no further bleeding disappearance of hematomas and some times an increase in reticulocytes In three patients tested

while on a scorbutic diet treatment with vitamin B_{12} folic acid or iron intravenously had no effect on the peripheral blood marrow or clinical condition (Fig 59) These three like all of the other patients then responded rapidly and completely to ascorbic acid When the anemia was severe enough a prompt reticulocytosis maximal between the fourth and sixth day occurred One patient given iron after ascorbic acid did not have a second reticulocyte response No change in the marrow followed treatment with iron vitamin B_1 or folic acid but when ascorbic acid was given the marrow became hyperactive with frequent mitosis and in two weeks was normal in appearance

Conflicting reports of the importance of vitamin C in erythropoiesis are probably attributable to the following facts anemia only occurs in severe degrees of scurvy both anemia and scurvy may be due to separate dietary deficiencies so that exclusion or association requires strict dietary control ascorbic acid has no proved effect other than antiscorbutic [and its ability to potentiate the hemopoietic activity of folic acid in scorbutic animals and patients —Ed] and the influence of hemorrhages other dietary deficiencies and metabolic requirements during clinical trials has not been recognized

[The mutual dependency in relation to hemopoiesis of ascorbic and folic acids probably explains the usual failure in our hands in the United States of ascorbic acid alone to promote hemopoiesis in scurvy In such patients possibly the folic acid deficiency is the controlling defect and not as here apparently the ascorbic acid —Ed]

OTHER ANEMIAS

Various aspects of several different kinds of anemias mainly due to diminished red cell production are described in the following articles The first three are concerned with congenital hypoplastic anemia at least some instances of which seem to be susceptible to relief by corticosteroids The article by Arrowsmith and his associates indicates a remarkable biochemical relationship between a steroid hormone and a vitamin in this condition —Ed

Congenital Hypoplastic Anemia During the past 15 years congenital hypoplastic anemia has emerged as a clinical entity characterized by progressive normochromic normocytic anemia beginning in early infancy with moderate leukopenia and bone marrow showing moderate hypoplasia of erythroid elements but with normal leukocytic and megakaryocytic centers E Omer Burgert Jr Roger L J Kennedy and Ger

trude L. Pease[7] (Mayo Clinic) report on 12 cases discovered among 214 patients with hypoplastic and aplastic anemias In 10 onset was before 7 months of age

In all cases red cell counts were below normal but fre quently previous transfusions had modified the initial counts which ranged from 650 000 to 4 090 000/cu mm Hemoglobin levels varied from 3 6 to 13 2 Gm /100 cc and were propor tional to the red cell values There was moderate hypochro masia in four cases but in the others the cells were normo chromic Polychromasia and evidence of regeneration were seen in only two patients who subsequently had remissions Leukocyte counts generally tended to be low ranging from 2 300 to 9 000/cu mm five children had levels below 4 500 Lymphocytes predominated in all and one boy had a slight eosinophilia (12 5%) There was a striking decrease or ab sence of reticulocytes and although one patient had 3 0% re ticulocytes the mean value for the others was only 0 3% Platelet counts varied from 25 000 to 409 000/cu mm and tended also to be at subnormal levels The two patients with very low platelet counts were a girl with hepatosplenomegaly and a boy with a bleeding tendency

Marrow was aspirated from the sternum of eight patients tibia of three and rib of one All specimens showed striking suppression of normoblasts maturation of which appeared to be arrested at the polychromatic stage In only two cases was the percentage of orthochromatic normoblasts greater than 0 5 In 13 of 14 marrow studies less than 5 8% of cells were normoblasts Myelopoiesis was active with no significant left shift Myeloid cells constituted 32 5 63 4% of cells Lym phocytes generally predominated values ranging from 30 6 to 63 6% but immature cells were not increased The marrow of eight patients was concentrated and that of six showed depression of myeloid erythroid layer In all 10 the myeloid erythroid ratio was elevated values ranging from 4 1 to 43 1

During the phase of recurrent anemia blood transfusions were required every three to eight weeks and was the only therapeutic measure of value antianemic treatment being ineffective In one case corticotropin therapy increased the reticulocytes from 1 0% to 3% In no case was splenectomy done

In five boys aged 17 months to 3 years spontaneous re

(7) P d t 13 218 2 6 M h 1954

mission occurred which lasted 20 months to about 8 years The other children aged 6½ 11½ years were maintained on blood transfusions Of all 12 patients 8 were alive at the last report The cause of two of the three known deaths was anemia Both patients had transfusion hemosiderosis

A child with congenital hypoplastic anemia will grow and develop normally as long as transfusions are repeated Spontaneous remission although unpredictable offers some hope Remission is less likely to occur in patients with hepatomegaly or splenomegaly

[For evidence of effective means of therapy see following articles —Id]

Erythrogenesis Imperfecta or Congenital Hypoplastic Anemia (Diamond Blackfan Type) O D Fisher and F M B Allen[8] (Queen s Univ Belfast) report a case

In a girl born in December 1949 pallor noted at age 3 months failed to respond to oral iron therapy She was the 12th child of a family with six miscarriages at six months and one stillborn full term child Only the 4th and 10th children survived and were healthy The pallor was intense at age 7 months and the spleen was palpable a blood transfusion was given At 14 months a second transfusion was required Results of blood examination were typical of congenital hypoplastic anemia hemoglobin 7 7 Gm /100 ml red cells 2 580 000/cu mm color index 1 0 white cells 7 450/cu mm platelets 220 000/cu mm reticulocytes less than 0 25% and serum bilirubin 0 2 mg /100 ml Leukocyte differential and red cell osmotic fragility were normal Results of the Coombs and Wassermann tests were negative Bone marrow showed normal myeloid series but marked hypoplasia of the erythroid series

Until about age 2½ the child required a transfusion approximately every two months folic acid vitamin B_{12} and liver extract preparations were without effect on peripheral blood or bone marrow Then corticotropin 10 mg every 6 hours intramuscularly for 14 days caused slight reticulocytosis and decreased the rate of fall of hemoglobin About 1½ months later cortisone 25 mg every 12 hours by mouth caused a reticulocytosis and the hemoglobin value continued to rise until in about 2 months it was 16 7 Gm /100 ml Cortisone was continued with final dosage 25 mg daily Intussusception developed with spontaneous reduction before laparotomy Postoperatively bone marrow examination revealed normal erythropoiesis Thereafter she required no blood transfusion and cortisone maintenance dosage was 12 5 mg every other day Hemoglobin content ranged between 11 8 and 13 75 Gm /100 ml

The authors reject the possibility of spontaneous remissions because of the reappearance of anemia with discontinu

(8) A ch. D s Childhood 28 363 368 O tober 1953

ance of cortisone and the high hemoglobin level achieved with the larger dose of cortisone They regard the action of cortisone as nonspecific or as possibly the result of endocrine deficiency for which there was no clinical evidence in this child Physical retardation has been reported by others as an inconstant feature of the condition

Production of Megaloblastic Marrow by Administration of Cortisone in Aplastic Anemia, with Subsequent Response to Vitamin B_1 is described by W R Arrowsmith Malcolm B Burris and Albert Segaloff[9] (New Orleans)

Child 18 months old with an aregenerative anemia limited to the red cell series had been under observation since age 4 months White cell and platelet values were normal but there was almost complete absence of reticulocytes from the peripheral blood Bone marrow was normal except for marked decrease in nucleated red cells When cortisone was admini tered reticulocytosis developed without significant rise in red cells However red cells became macrocytic and marrow examination then showed many megalo blasts Thereupon administration of vitamin B_1 and folic acid produced a second reticulo ytosis with a rise in hemoglobin content. When cortisone was discontinued despite administration of vitamin B_1 and folic acid anemia returned Readministration of cortisone together with vitamin B_1 and folic acid caused another reticulocyte response with rise in red cell level Splenectomy after all therapy was discontinued did not prevent recurrence of anemia which was again abolished by administration of cortisone and vitamin B_{12} with a reticulocytosis of 40% and return to hemoglobin level of 13 0 Gm % After six months this therapy was discontinued with only partial relapse of the anemia

Apparently under the influence of cortisone erythropoiesis in the marrow progressed to the megaloblast stage but no fur ther unless vitamin B_1 was given

***Hypoplastic Anemias and Related Syndromes Caused by* Drug Idiosyncrasy** are discussed by Edwin E Osgood[1] (Univ of Oregon) Hypoplastic anemia is characterized by the occurrence of erythrocytic granulocytic and thrombocytic hypoplasia singly or in combination Lymphocytes may also be decreased and the marrow shows a corresponding decrease of the peripherally deficient element In the absence of aleu kemic leukemia a total nucleated cell count of less than 6 000/ cu mm in aspirated bone marrow is diagnostic

Drug idiosyncrasy hypoplasias are more common in aller gic persons and with a second or an intermittent course of

(9) J Lab & Cl M d 42 778 N mb 1953
(1) J A M A 152 816 818 J 27 1953

treatment The mechanism of idiosyncrasy is unknown Known facts are best explained if the drug or one of its metabolites in susceptible persons is assumed to combine with an essential protein of the cell to form a new protein that causes development of antibodies The severity is unrelated to the amount of drug taken These hypoplasias must be differentiated from mild hypoplasias of infection hypothyroidism and hypoproteinemia erythropenia of impaired renal function moderately severe hypoplasias secondary to hypersplenism (an enlarged spleen is important) congenital hypoplasias myelofibrosis and osteopetrosis idiopathic hypoplasia hypoplasias due to myelotoxic agents and hypoplasia that appears terminally in some cases of lymphocytic leukemias A history of all drugs taken for the preceding four to eight weeks is important

Normocytic anemia usually develops last because of the long life of the red cell however reticulocytes decrease early Anemia alone can be treated by one transfusion every 7 10 days Granulocytopenia with 500 neutrophils/cu mm or more is mild Moderate asymptomatic granulocytopenia should be treated with 300 000 units of procaine penicillin and 0 5 Gm streptomycin a day Patients with severe granulocytopenia of *200 neutrophils/cu mm or less or symptomatic* granulocytopenia of any magnitude should be treated with large doses of antibiotics for at least one week after signs and symptoms have subsided then maintained on a prophylactic dose Thrombocytopenia is associated with the usual bleeding manifestations and is best treated with fresh blood transfusions every six hours until clot retraction begins in one hour It may be necessary to support these patients for many months before spontaneous recovery which is the rule A trial of cortisone or corticotropin may be justified Cobalt chloride is effective in some erythrocytic hypoplasias

Drugs known to carry a greater risk than the disease treated should be avoided If these drugs (table) are used hemoglobin level white blood cell and reticulocyte counts and clot retraction time should be obtained at repeated intervals Appearance of *mild abnormalities calls for daily observations* Any progression of the abnormality or an initial moderate abnormality calls for cessation of therapy Once a

CLASSIFICATION OF DRUGS THAT MAY PRODUCE IDIOSYNCRASY CAUSING HYPOPLASTIC ANEMIA OR RELATED SYNDROMES

C assific n	E m t Rela R s ‡
Anticonvulsants	
Methyl phenyl ethyl hydantoin (me antoin®)	High
Trimethadione (tridione®)	Mod
Antihistamines*	
Phenothiazine type (phenergan®)	Mod
Ethylenediamine type (pyribenzamine® hydrochloride)	Low
Antimicrobial agents	
Arsenobenzol	High
Chloramphenicol	High
Sulfonamides	Mod
Thiosemicarbazone* (tibione®)	Mod
Streptomycin	Low
Antithyroid agents	
Thiouracil *	High
Methimazole (tapazole)	Mod
Sedatives	
Allylisopropylacetylurea† (sedormid®)	High
Aminopyrine* (pyramidon®)	High
Phenacemide (phenurone®)	Mod
Pyrithyldione (presidon®)	Low
Spasmolytics	
Phenothiazines* (diparcol)	Mod
Procaine amide (pronestyl) hydrochloride	Low
Unclassified group	
Gold preparations	High
Phenylbutazone (butazolidin®)	High
Nitrophenols*	High
Mercurial diuretics	Low
Quinidine†	Low
Quinacrine hydrochloride (atabrine® d hydrochloride)	Low

* Ch fly g l cyt hyp pl
† Ch fly th mb cyt hyp pl
‡ E ed n p p tion f p son g drug wh m f th hypo- pl t y d m lik ly to d l p N l q t d ta l ble ex pt f q f r wh h k pp m t ly 1 n 25 000 p t t y f p e.

patient has recovered he should never again receive the offending drug

Much remains to be learned about the relative risks of various drugs and the pathophysiology of the disease It is suggested that physicians report all instances of drug induced hypoplasias to the Council on Pharmacy and Chemistry of the American Medical Association [Forms are now available on request for this purpose —Ed]

Physiologic Evaluation and Management of Chronic Bone Marrow Failure Virgil Loeb Jr Carl V Moore and Reubenia Dubach (Washington Univ) evaluated the erythropoietic

(2) Am J Med 15 499 517 O t b 1953

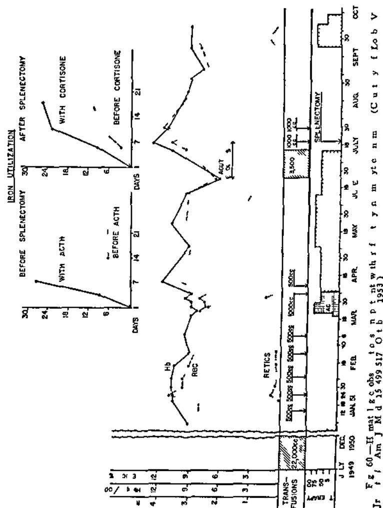


Fig 60—H mat l g c obs t o s n p t nt w th r f t y n m yte n m (C u t y f L o b V Jr et al Am J Med 15 499 517 Oct 1953)

equilibrium of 11 patients with chronic bone marrow failure using new physiologic technics in addition to the usual hematologic data derived from blood and bone marrow examination The radioactive iron utilization test was used to measure the efficiency of iron utilization in hemoglobin synthesis This involves injection of 5 15 mg radioactive iron as ferrous ascorbate and estimating the amount of tracer dose in the

red cells in two weeks In the normal subject at least 75% of the dose should be in the red cells in this period Serum iron and iron binding capacity were also measured The presence or absence of a hemolytic component was detected by estimating the hemoglobin catabolism as reflected in the fecal urobilinogen excretion hemolytic index and survival time of transfused red cells The anemia was characterized by reticulocytopenia and poor iron utilization No correlation between marrow morphology and erythropoietic function was found

Two patients brothers aged 22 and 26 had an extreme degree of erythroid hypoplasia (erythrogenesis imperfecta) In the elder a hemolytic component appeared with hemosiderosis and hepatosplenomegaly after five years of treatment with multiple transfusions In this patient ACTH evoked a striking erythropoietic response and splenectomy was advised After operation hemolysis ceased and there was transient marrow recovery Subsequently cortisone had to be given for several months after which complete recovery ensued and has lasted for 19 months The younger brother showed no evidence of hemolysis but a familial disorder was suspected After a marrow response to ACTH was established splenectomy was carried out Complete recovery ensued and has lasted 29 months

Three patients with myelosclerosis two of whom also had myeloid metaplasia had a marrow response to ACTH In two showing increased hemolysis splenectomy was carried out with return to normal or near normal hematologic levels without further treatment The unsplenectomized patient has remained well on a maintenance dose of cortisone

The other six patients had refractory anemia with a normally cellular bone marrow as illustrated by the following case

CASE 5 —Woman 57 had refractory normocytic anemia and had been treated by transfusions 500 ml blood about every two weeks for two years before being studied There was a moderate anemia with no splenomegaly or evidence of increased hemolysis The survival time of transfused red cells was normal Bone marrow was of normal cellularity with an increase of normoblasts and an occasional multinucleated red cell There was decreased radioactive iron utilization On ACTH and later cortisone therapy iron utilization improved (Fig 60) The patient began to feel better but after three months of treatment evidence of acute hemolysis necessitating transfusions suddenly appeared Splenectomy was carried out and

the fecal urobilinogen excretion fell Further transfusions were not required but the red cell count and hemoglobin content decreased slowly and iron utilization was poor Cortisone therapy led to im provement but had to be stopped because of edema and hypertension The blood picture deteriorated and transfusions were again required Several months later the patient died of pneumonia and acute hepatitis Autopsy was not permitted

In all 10 patients with chronic bone marrow failure showed increased erythropoiesis on ACTH or cortisone ther apy *This demonstration of latent potentiality to produce* more blood cells was regarded as an indication for splenec tomy A hemolytic component probably due to increased phagocytosis or stasis in a spleen altered by a transfusion induced hemosiderosis or enlarged by extramedullary hemo poiesis was when present an additional indication Because a patient with complete erythropoietic failure requires no more than one 500 cc transfusion every 7 10 days to maintain a constant red cell level splenectomy in a patient with a greater transfusion requirement due to hemolysis may reduce this requirement Further the possibility of splenic inhibition of the bone marrow was considered A favorable influence of ACTH or cortisone on iron utilization was uniformly an indi cation that splenectomy would be beneficial

Splenectomy was done on eight patients five of whom had excessive hemolysis Two were only slightly improved but in six recovery when viewed against the background of the only alternative—frequent multiple transfusions and limited phys ical activity—was dramatic All patients who received trans fusions had hemosiderosis

[One additional index of erythropoietic activity the plasma radio-active *iron clearance rate was not available to these authors This is an* important and critical report on a problem of great therapeutic difficulty —Ed]

Acute Erythroblastopenia Due to Anuria G Richet D Alagille and E Fournier[3] (Paris) report the results of 35 myelographic studies on 21 patients with acute renal insuffi ciency Regardless of whether the cause of anuria was infec tious toxic or mechanical marrow specimens obtained from these patients by sternal puncture showed a selective but temporary disappearance of erythroblasts In striking con trast to the persistence shown by the megakaryocytes and the active development of myeloid cells disappearance of

(3) P esse méd 62 50 53 J n 13 1954

erythrocytic elements which begins about the fifth day and lasts for a month or more is almost complete Nucleated red cells when present are normal in structure

This peculiar disturbance in the erythropoietic process apparently occurs only in patients with acute renal insufficiency and has never been noted in those with chronic nephritis and long standing azotemia even in the terminal stage The results of the disturbance can be seen in the prolonged secondary anemia so evident during convalescence from acute anuria Despite an adequate diet and the absence of pathologic hemolysis regular transfusions may be needed to maintain the red cells at an acceptable level until the young elements of the erythrocyte line reappear in the marrow and normal erythropoiesis is resumed

[This interesting observation should stimulate study of bone marrow in such patients by others —Ed]

Gaucher's Disease Clinical Features and Indications for Splenectomy Report of Five Cases of this rare familial disease characterized by accumulation of the cerebroside kerasin in the cells of the reticuloendothelial system is made by Alfred E Leiser and John D Battle Jr [4]

CASE 1 —Girl 7 Jewish was seen because of splenomegaly and hepatomegaly observed during a routine examination one year previously Results of blood liver and x ray studies were normal Marrow aspiration was not permitted but review of a specimen obtained the previous year showed it to be normal Banti s syndrome was diagnosed provisionally Two years later marrow from the iliac crest showed many typical Gaucher cells On follow up two years later there had been no recent changes in blood or spleen

CASE 5 —Man 39 Italian was seen because of splenomegaly discovered at a routine examination several months previously Examination disclosed hepatomegaly mild anemia 2 600 white blood cells/cu mm. and a moderately decreased platelet count. Typical Gaucher cells were found in the sternal marrow (Fig 61) There were 3 3% reticulocytes and the icterus index was 9 units Roentgen study disclosed femoral lesions

Two clinical courses of the disease have been described the infantile with a fulminant course and central nervous system involvement and the adult type with a prolonged chronic course The cases seen by the authors indicated that the disease may occur at any age and progress slowly often with minimal symptoms Splenomegaly is characteristic and in three cases led to diagnosis This feature should be remem

(4) Cl la d Cl n Q rt 21 6 13 J n ry 1954

bered in a differential diagnosis of myeloid metaplasia of the spleen chronic leukemia and malignant lymphoma Bone lesions are often detected and bone pain and occasionally pathologic fracture occur The long bones spine pelvis and skull are most commonly involved There is often a mild to moderate normocytic normochromic anemia granulocytopenia is common and thrombocytopenia, sometimes sufficient to cause hemorrhagic symptoms is frequently seen In



F g 61—G h cell f om st rnal m rr w Note large s e of lls a d wr nkl d t p p pp c f cyt plasm (Courtesy f Le e A E d Battle J D Jr Cl l nd Cl Q t 1 6 13 Jan ary 1954)

some cases reticulocytosis and an elevated serum bilirubin level may suggest that the anemia is in some part hemolytic

In some cases hematologic changes are probably due to infiltration of the marrow by Gaucher cells whereas in others the occurrence of pancytopenia in the presence of hypercellular marrow may implicate a secondary hypersplenism

Splenectomy is warranted when the increased size of the organ leads to distressing symptoms but not as a measure to avoid spontaneous rupture It is beneficial in patients with pancytopenia and a hypercellular marrow if hemolytic anemia or hemorrhagic symptoms are present Mild hypersplenism is

not an indication Failure to improve after splenectomy is due to irreversible marrow replacement rather than to hyper splenic effects Splenectomy does not arrest the disease pancytopenia and bone lesions sometimes appearing after op eration Although one author reports several cases in which the patients survived more than 15 years after splenectomy and in one case 31 years this report does not prove that the operation increases the life span of patients with Gaucher s disease

Gaucher s Disease in 29 Cases Hematologic Complications and Effect of Splenectomy To determine the incidence and nature of this hematologic abnormality and assess the value of splenectomy Alan S Medoff and Edwin D Bayrd[5] (Mayo Clinic) reviewed 29 cases diagnosed on the basis of sternal marrow aspiration splenic puncture study of the ex cised spleen or autopsy Fourteen of the 29 patients were male ages were 2½ 56 years 9 were over 40 16 were Jewish 5 were American and the rest (1 each) of Polish German Peruvian Greek or Italian lineage One patient gave a familial history of the disease six others mentioned splenomegaly of unknown origin in some member of the family

Onset was always gradual beginning with weakness and fatigue accompanied later by splenomegaly hepatomegaly and skin changes In 12 cases easy bruising and epistaxis were presenting symptoms Most complaints were referable to splenomegaly initially painless and later always distressing Hepatomegaly noted in 23 cases was less constant Brom sulfalein clearance was normal but the indirect serum bilirubin test often disclosed a slightly raised level and the direct re action was noted once Other abnormalities included skin pig mentation in 11 pinguecula in 9 and lymphadenopathy in 1 X rays disclosed skeletal changes in 15 cases usually in distal ends of the femurs but also in the tibia humerus radius and vertebrae Pathologic fractures of the vertebra rib and hip were reported in three cases

Hematologic abnormality was noted in 24 patients (sec ond in incidence only to splenomegaly) Most common was anemia usually hypochromic moderate in 21 and severe in 3 with 2 666 000 red cells/cu mm the lowest value Fewer than 5 000 leukocytes/cu mm were seen in 13 cases—lowest value

(5) A I t M d 40 481 492 M h 1954

1 500 The differential count was not remarkable Thrombocytopenia (fewer than 100 000 platelets/cu mm) was noted in 13 patients—the lowest count 16 000 Thrombocytosis was only encountered after splenectomy In nine patients all three elements were depressed in seven two were depressed and in eight others one was depressed Of the 12 patients who complained of easy bruising 8 had thrombocytopenia there was slight evidence of increased hemolysis

Splenectomy was done in 15 patients to relieve discomfort or hypersplenism Two died postoperatively the others were relieved of pressure symptoms and anemia leukopenia or thrombocytopenia was corrected for sustained periods In only one case were hemoglobin and red cell values lower than preoperatively but even then leukocyte and platelet counts remained elevated Of 14 patients who did not have splenectomy one was alive 12 and two others 14 years after initial visit Of the 15 whose spleens were removed 2 were alive 20 years later and 1 each 16 14 13 and 11 years after initial visits The follow up was complete in only 21 cases

Anemia in Bacterial Endocarditis William B Parsons Jr Talbert Cooper and Charles H Scheifley[6] (Mayo Clinic and Found) reviewed 200 cases of bacterial endocarditis proved by blood cultures or at autopsy and compared the incidence of various clinical features with that of anemia and other blood findings

At least 14% of the patients had been regarded as anemic before coming to the Clinic and had been treated ineffectively with iron or liver Some had received transfusions Hemoglobin levels below 12 Gm /100 cc in males and 11 Gm in females are considered indicative of anemia The initial hemoglobin values of 150 patients were below these levels 7% had values between 13 and 15 Gm and 14 1% values less than 9 Gm No consistent relation could be established between hemoglobin levels and duration of the disease In 45% of patients the red cell count was more than 4 000 000/ cu mm it was between 3 000 000 and 4 000 000 in 45% and less than 3 000 000 in 9 4% The anemia tended to be slightly hypochromic although in many instances the cells were normochromic In blood smears the commonest red cell abnormalities were increased regeneration increased rouleaux forma

(6) J A M A 153 14 16 Sept 5 1953

tion and hypochromasia The erythrocyte sedimentation rate was greater than 30 mm in one hour in 92.6% of patients Leukocyte counts of over 10 000/cu mm were recorded for only 36% Toxic granulation and myeloid immaturity were frequently seen in the smears In 37 cases reticuloendothelial cells were seen in smears with evidence of phagocytosis in 11 This incidence might have been greater had smears been made from the first drop of blood from the ear lobe in all cases

Anemia in bacterial endocarditis was exceeded in frequency only by cardiac murmurs and positive blood cultures and was more frequent than evidence of embolism (61%) splenomegaly (44%) cardiac enlargement (37%) and finger clubbing (17%) The incidence of the various clinical features is perhaps lower than that reported in previous reviews but all these patients were seen at an early stage of the disease and are considered from a clinical rather than a pathologic viewpoint

The occurrence of an unexplained anemia with fever should always suggest bacterial endocarditis as murmurs are not invariably present Further some patients under inadequate antibiotic therapy may be apyrexial and have a negative blood culture Here anemia may be an important guide especially if accompanied by a murmur however the practice of attributing a soft systolic murmur to anemia may be misleading Another useful confirmatory finding is the demonstration of phagocytic reticuloendothelial cells in the first drop of blood from the ear lobe although this may be seen in other conditions [such as chronic infections or acquired hemolytic anemia —Ed]

POLYCYTHEMIA

Polycythemia Leukoerythroblastosis and Myelosclerosis J W Beattie and J L Withey[7] report three cases of polycythemia vera which progressed to myelosclerosis

CASE 1—Woman 69 complained for a year of pain in the back hips and legs and an aching mass in the left side Blood studies showed 5 920 000 red cells/cu mm hemoglobin 113% and 11 600 white cells 13% being immature granulocytes A few nucleated red cell were seen Four years later when she was readmitted with

(7) B M J 414-417 Aug 2 1953

pain and increasing weakness liver function and x rays of bone were normal However blood studies showed 3 100 000 red cells/cu mm hemoglobin 66% and 7 000 white cells 11 5% being immature granulocytes Marrow biopsy showed myelofibrosis with increased numbers of megakaryocytes

CASE 2—Woman 48 complained of recent epigastric pain back ache and vomiting The blood showed 8 500 000 red cells/cu mm hemoglobin 122% and 9 100 white cells all mature forms There was splenomegaly and irradiation of the spleen was beneficial After 12 years observation she required treatment for anemia blood values being 2 500 000 red cells/cu mm hemoglobin 48% and 4 200 white cells with 8% immature granulocytes Several nucleated red cells were seen Sternal marrow was poorly cellular and rib biopsy showed myelofibrosis

CASE 3—Man 51 with recurrent gout and a left subcostal mass for two years when first seen had blood values of 5 600 000 red cells/cu mm hemoglobin 120% and 13 600 white cells 12% being immature granulocytes In the next five years the spleen was irradiated three times On hospitalization for severe splenic pain and acute gout blood values were 3 400 000 red cells/cu mm hemoglobin 64% and 9 200 white cells 21% being immature granulocytes Nucleated red cells were seen Marrow biopsy showed myelofibrosis On death six months later autopsy revealed marked osteosclerosis of the ribs fibrosis of the vertebral marrow and hemopoietic foci in spleen liver and kidneys

These cases are very similar to many described in the literature The late occurrence of anemia in polycythemia has often been noted some reports describing a leukoerythroblastic state during which myelosclerosis was diagnosed and myeloid metaplasia of the spleen was common Although authors tend to stress some characteristic feature of their cases by careful perusal of the numerous reports the syndrome can be fairly well defined and although there is no lack of etiologic theories most agree that it is quite distinct from myeloid leukemia The characteristic extramedullary hemopoiesis cannot be regarded simply as compensatory to marrow sclerosis since it is associated with diverse clinical states unrelated to bone disease Moreover it is not nearly so marked in more severe and persistent anemias [Wyatt and Sommer s patients had splenomegaly at a time when the marrow was still cellular preceding the fibrosis—Ed] Rather extra medullary hemopoiesis is a dynamic process a response to some stimulus probably the same as that which causes the fibroblasts (and osteoblasts) to produce myelosclerosis This stimulus is possibly a nutritional deficiency or some abnormal metabolite

Leukemoid Blood Reactions Schuyler V Hilts and Christopher C Shaw[8] (U S Naval Hosp Oakland Calif) report two cases Earlier it was believed that leukemoid reactions could be differentiated from leukemia by peripheral blood examination with particular reference to the development of thrombocytopenia anemia and basophilia in true leukemia Recent studies have demonstrated that bone marrow examination is the only certain method of differential diagnosis of these conditions

CASE 1—Youth 19 with acute glomerulonephritis had four leukemoid episodes The first coincided with a phase of pulmonary edema and anemia white cell count rising to 33 600/cu mm with 6% juvenile and 8 band forms 46% polymorphonuclears and 40% lymphocytes Subsequent crises were chiefly myelocytic one occurring during a clinical remission following extensive antibiotic therapy At thi time there were 32 500 white cells/cu mm 1% being myelocytes 9% juvenile and 9% band forms 63% neutrophil polymorphonuclears 7% eosinophils 10% lymphocytes and 1% monocytes Another peak followed the injection of 200 or 300 ml hemolyzed blood from an extracorporeal dialysis apparatus The 27th day accompanied by anemia pulmonary edema and rising blood urea content white cell count rose to 51 900/cu mm with 11% myelocytes 2% band forms and 87% polymorphonuclears and he died

CASE 2—Youth 20 with suspected tuberculosis and anemia had leuko yte count of 32 000/cu mm with 14% myelocytes 13% juvenile form 16% stab cells 45% polymorphonuclears 10% lymphocytes and 2% mono ytes On clinical grounds and becau e of conversion of a positive PPD tuberculin rea tion to negative treptomycin and p amino alicylic acid were given with little response Leukocytosis persisted and marrow obtained at biopsy was typical of leukemoid reaction Despite this chronic myeloid leukemia was diagnosed when the white cell count rose to 60 000/cu mm with 16% myelocytes 7% juvenile form 8% stab cell 63% polymorphonuclears and 6% lymphocytes Urethane therapy was begun and in five weeks there was pancytopenia confirmed by marrow biopsy At this time miliary tuberculosis was demonstrated by x rays and later meningitis supervened Ju t before death white cell count rose to 22 800/cu mm with 1 band forms 94% polymorphonuclears and 5% lymphocytes

The variety of clinical states associated with leukemoid blood reactions have led to many theories of its production

(8) N w E gl d J M d 249 434 438 S pt 10 1953

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Poorly differentiated tumors with tendency to extensive necrosis are frequently discovered in such cases

Knowledge of the existence of these leukocytoses is significant in differential diagnosis Simultaneous occurrence of a malignant tumor and myelosis is not common The author s opinion is that a hyperleukocytosis with immature white cells

INCIDENCE OF LEUKOCYTOSIS (OVER 20 000) 1949 52

	20 000 30 000	30 000 40 000	Over 40 000
Myelosis and lymphadenosis	6	5	39
Coccic infections and tuberculosis	40	5	—
Acute infections	31	8	—
Malignant tumors	11	1	—
Cardiovascular diseases	10	—	—
Metabolic disturbances (diabetic and hepatic coma)	7	3	—
Blood dyscrasias and acute hemorrhages (excluding leukemias)	7	1	—
Intoxications (CO and hypnotics)	3	—	—
Total	115	23	39

in the presence of a malignant tumor is not indicative of the simultaneous presence of a myelosis The quality of the cells together with the clinical picture determines the diagnosis

Failure of Antibiotic Therapy in Infectious Mononucleosis Stuart H Walker[1] (Western Reserve Univ) conducted therapeutic trials in 78 patients with infectious mononucleosis In group 1 21 patients *not in the controlled study* were treated with chlortetracycline In group 2 14 patients were treated with chloramphenicol In group 3 11 patients who formed part of the controlled study were treated with chlortetracycline In group 4 10 patients who formed part of the controlled study were treated with placebo In group 5 22 patients were treated symptomatically or with penicillin During the study all patients hospitalized with infectious mononucleosis were allocated by a prearranged code to either group 3 or group 4 Some patients in other groups received sulfonamides in addition to the agent being tested but these drugs were disregarded in the study in view of their reported inefficacy in this disease

Diagnosis was based on the clinical picture and the presence of a significant titer (1 128 or higher) of heterophil antibodies with 10% or more atypical lymphocytes in the

(1) Am J F Sc 26 57 July 1953

and three basic mechanisms have been suggested stimulation of the marrow by infection mechanically or by antigen antibody reaction response of the marrow to great demand or ectopic hemopoiesis secondary to a prolonged demand on or obliteration of the bone marrow Recent work on the fate of transfused lymphocytes suggests that the lungs are the site of removal of leukocytes from the blood Consequently failure of the normal mechanism may produce high leukocyte counts Thus a leukemoid reaction may be explained by a disorder of the lungs such as edema and infection The multiple peaks of the leukocyte count in Case 1 preclude any single explanation but involve such factors as anemia pulmonary edema hemoglobinemia and azotemia Case 2 may support the theory of lung damage [or of infection with marrow involvement —Ed]

Marked Leukocytosis in Carcinoma L Hensler[9] (St Gallen Switzerland) reviews the literature and reports a case

Man 65 was hospitalized in poor general condition There were bilateral supraclavicular and left axillary enlarged lymph nodes and a hard tumor in the right axilla The lungs had bilateral discrete moist rales Liver and spleen were normal Cerebrospinal fluid and urine showed no abnormalities There was bilateral mild pretibial edema The red blood cell count was 3 880 000 and the hemoglobin level 70% with color index 0 9 The leukocyte count was 49 000 with 9% stab forms 82% segmented forms 1% eosinophil 1% basophils 1% monocytes and 6% lymphocytes The cells were predominantly mature with orthochromic cytoplasm and prominent granules There were many blood platelets X ray examination showed a large infiltrate in the upper part of the left lung over the hilus There were small multiple infiltrates in the rest of the lung fields Needle biopsy of the axillary tumor showed carcinoma tissue Despite x ray therapy the lymph nodes enlarged the cachexia became progressive and the leukocyte count rose to 67,900

Autopsy disclosed an apple sized carcinoma of the left kidney There were metastases to all parts of the lungs thyroid liver adrenals abdominal lymph nodes and other organs There were osteolytic metastases in the first second and third lumbar vertebrae Microscopically a carcinoma solidum simplex with large areas of necrosis was found The bone marrow especially the myeloid system showed a reactive hyperplasia

Marked leukocytosis accompanying large tumors is well known (table) In the absence of a secondary infection or active bleeding it is considered an abnormally strong reaction of the bone marrow The reason for this reaction is not clear

(9) S hwe z m d W h sch 83 1032 1034 Oct 24 1953

material from the cavity For agglutination tests 1 drop of leukocyte suspension was added to 1 drop of serum on a siliconized slide the drops mixed and the slide incubated for one hour at 37 C then examined microscopically for evidence of agglutination

Intracardiac injections of antileukocytic serum produced transitory leukopenia with secondary marrow stimulation Repeated injections produced prolonged granulocytopenia

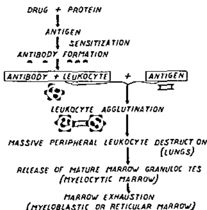


Fig 6 —(C t y f Moeschl S t l A t h m t 11 73 94 1954)

and in the bone marrow an increased number of immature forms and enlarged cell size No morphologic changes in the leukocytes of the peripheral blood no cellular phagocytosis nor destruction of cells in the marrow was noted

The serum produced striking leukocyte agglutination in vitro without lysis and in vivo was a potent leukopenic agent Through absorption of the serum with leukocytes the leukopenic and agglutinative properties could be eliminated thus suggesting that these properties are an entity or at least closely bound This substance was noted in the T wave electrophoretically and could be transmitted through the placental barrier in the rabbit Leukopenia is apparently produced by agglutination of leukocytes peripherally with subsequent destruction and removal from the circulation in small lung capillaries With use of P labeled leukocytes and cross transfu

peripheral blood To evaluate progress day to day observation was made of the rectal temperature physical signs of the disease (e g pharyngitis lymphadenopathy hepatosplenomegaly) and hepatitis as assessed by the cephalin cholesterol flocculation test *The disease was considered to progress if a sign increased in severity or a new sign appeared 24 hours* after therapy was begun Relapse was recorded when exacerbation occurred after a 24 hour period without signs

Accumulated data showed no difference in the course of the disease in untreated patients and in those treated with chloramphenicol and chlortetracycline These agents may have conferred slight benefit but certainly no dramatic effect was observed Repeated pharyngeal cultures failed to incriminate any respiratory organism as causative The severity of infectious mononucleosis complications has led in recent years to the introduction of multiple therapeutic agents Conflicting reports of their value are probably due to the variability of the disease and its frequent termination by crisis *Despite favorable reports on chloramphenicol and chlortetracycline* in infectious mononucleosis it seems that these too must join the list of ineffective therapeutic measures

Experimental Agranulocytosis Its Production through Leukocyte Agglutination by Antileukocytic Serum is reported by S Moeschlin H Meyer L G Israels and E Tarr Gloor[2] (Univ of Zurich) Previous observations had suggested that agranulocytosis of anaphylactic or infectious immunologic origin is produced by agglutination and destruction of circulating leukocytes With use of an antileukocytic serum which can produce leukocyte agglutination in vitro varying degrees of agranulocytosis were produced in the guinea pig

TECHNIC —Leukocytes from the peritoneal exudate of the guinea pig were washed in saline *contaminating red cells lysed by 0 33% acetic acid and then washed again Into rabbits were injected* 5 ml doses of leukocyte suspension (500 000 cells/cu mm) at five to seven day intervals for four to six weeks Blood was withdrawn and serum separated and stored at —20 C This serum sometimes contained a hemolysin which could b removed by inactivating the complement then adsorbing it twice on washed guinea pig red cell The serum was injected in 0 25 1 0 ml doses intracardially into guinea pigs Leukocyte counts were made at *5 10* minute intervals for an hour and at longer intervals thereafter Bone marrow specimens were obtained by trephining the femur and scooping out the

(2) A ta ba m t 11 73 94 1954

known whether synthetic antithyroid drugs had been used In none of the cases could infection be considered a causative factor

Serologic studies showed that the leukoagglutinins contained in the serum of these three patients were thermostable resisting heating for a half hour at 56 C and being destroyed by heating for a half hour at 65 C They were more effective at 37 C than at 18 C or 4 C They were effective in both saline and serous mediums and at pH s ranging from 65 to 92 Absorption and elution tests proved that they could be completely absorbed by normal leukocytes and that they subsequently reappeared in the eluate Fixation did not result in consumption of complement Electrophoretic study showed a remarkable increase in gamma globulin in all three serums All kinds of human leukocytes were agglutinated by these substances without any apparent specificity for a particular line

Discovery of these agglutinins completes the triad of nonspecific substances producing agglutination of the three formed elements of human blood—erythrocytes thrombocytes and leukocytes The immunologic nature of the newly discovered substances though not yet definitively established is highly probable In all likelihood they represent antibodies capable of acting on antigens carried by human leukocytes

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LEUKEMIAS AND RELATED DISORDERS

Panmyelosis and Chronic Granulocytic Leukemia Bernard Black Schaffer and Leland D Stoddard[4] (Duke Univ) reexamined data in 19 cases diagnosed as acute or chronic myelogenous leukemia On the basis of pathologic anatomy alone at least three different categories appeared In eight the diagnosis of chronic myelogenous leukemia was justified by a similar pattern throughout There was a relatively uniform bone marrow hyperplasia in which myelocytes were overwhelmingly prominent and nongranulocytic hemopoietic elements were diminished or even absent The splenic parenchyma was partially replaced by leukemic cells The liver sinusoids and portal fields were involved the latter exten

(4) *Am J P th* 29 413-449 M y J e, 1953

sion agglutinated leukocytes failed to reappear in the blood and the leukocytes which did appear in the blood were chiefly staff forms obviously derived from marrow Lytic or phagocytic effects could not be demonstrated

After peripheral destruction of leukocytes the demand on the bone marrow increases with early decrease of mature forms and moderate hyperactivity of the granulocytic series When leukocyte destruction is long protracted the marrow changes are more striking with a pronounced shift to the left and young basophilic cells preponderate should destruction continue marrow granulopoiesis may be exhausted This aplastic reaction is analogous to that of erythroplastic elements in severe hemolytic reactions and of platelet formation in severe acute thrombocytopenias The longer maturation time and shorter life of the granulocytes may explain the greater sensitivity of the granulopoietic system

The concept that agranulocytosis is an effect of increased leukocyte destruction by immune bodies (Fig 62) parallels that regarding such other immunocytopenias as hemolytic anemia and thrombocytopenia Other granulopenias (e g in disseminated lupus erythematosis Felty s sydrome rheumatic fever and infectious mononucleosis) may also be immunologic and this concept may be extended to include some forms of cyclic agranulocytosis transitory leukopenias of the newborn and hypersplenism

Presence of Leukoagglutinin in Serum of Three Leukopenic Patients J Dausset A Nenna and H Brecy[3] (Paris) report the discovery of a leukoagglutinin capable of agglutinating all normal leukocytes directly without the intervention of a substance against which the patient is sensitized The leukoagglutinin which was first detected in the serum of a woman with fatal agranulocytosis probably caused by aniline poisoning has since been demonstrated in the serums of two other patients with leukopenia One of these died of a cirrhotic syndrome and the other had chronic medullary hypoplasia Although there was no direct evidence of any leukopenia producing intoxication in the histories of these two patients one had been treated for rheumatic pains with large quantities of salicylic acid over a long period and the other had received treatment for hyperthyroidism though it was not

(3) Sang 24 410 417 1953

produced by metastatic tumors and other bone marrow re placements

In panmyelosis splenectomy or splenic irradiation does not necessarily lead to anemia agranulocytosis and thrombo cytopenia freedom from these complications was observed in these cases In the evaluation of therapeutic measures in myelosis panmyelosis must be differentiated from chronic myelogenous leukemia since the former has a duration of 11 112 months compared to 14 20 months in leukemia

[But it is possible that chronic myelogenous leukemia was still the proper etiologic diagnosis in these 19 cases In some the slower progress of the same disease may permit the evolution of the pathologic sequences of hyper to hypocellularity with later fibrosi or osteosclerosis of the marrow Clinically at least there may be as much difference between acute and chronic myelogenous leukemia as between chronic leukemia and panmyelosis —Ed]

Treatment of Patients with Myelosclerosis is described by R A Hickling[5] (Charing Cross Hosp London) Unless new bone formation in the marrow has occurred (osteosclerosis) which can be detected by x ray examination fibrosis of bone marrow can be proved in life only by biopsy of a bone in which red marrow is normally present Needle puncture is not reliable Although myelosclerosis is commonly attended by severe anemia patients usually seek advice because of ab dominal discomfort due to an enlarged spleen the general health being unaffected They should be urged to tolerate the disability for eventually general symptoms appear which preclude further postponement of x ray therapy X ray ther apy to the spleen and affected bones causes the malaise and lassitude to disappear the spleen to diminish in size and the number of leukocytes mature and immature in the blood to decrease This effect varies in duration and is less pronounced on succeeding courses

Four patients with osteosclerosis and five with myelo sclerosis were studied and seven of the eight deaths followed by autopsy in the eighth only liver and spleen being exam ined after death Two patients did not receive x rays one had acute leukemia with leukopenia and the other was severely anemic The latter had no increase of circulating leukocytes but many were immature and megakaryocytes were common Both responded poorly to transfusions

Of the seven treated by x rays two derived no benefit

(5) B M J 411 414 Aug 22 1953

sively The lymph node structure was altered by granulocytic proliferation Massive proliferation was also seen in viscera not associated with extramedullary hemopoiesis Erythrogenic tissue and megakaryocytes were scarce or absent

Seven cases were examples of panmyelosis and in four there was a related myelofibrosis In those without myelofibrosis diffuse bone marrow hyperplasia was characterized by numerous megakaryocytes granulocytes erythroid cells fibroblasts and sometimes osteoblasts To this picture was added in myelofibrosis reticulum cells and small foci of fine reticulin network In more severe fibrosis lymphocytes and plasma cells appeared and hemopoietic islands were often split up by reticulin fibers Osteosclerosis was sometimes seen The spleen was always enlarged similar pleomorphic hemopoietic foci being prominent In the liver these foci resembling marrow and containing megakaryocytes were well marked in the sinusoids but there was little or no involvement of the portal fields Lymph nodes were small containing pleomorphic hemopoietic foci Other viscera were uninvolved or only minimally so

Four cases were transitional between panmyelosis and chronic myelogenous leukemia One was a clear case of panmyelosis except for obliteration of the structure of some lymph nodes by granulocytes as in leukemia Two cases were examples of panmyelosis and osteosclerosis associated with acute granulocytic leukemia Foci of pleomorphic hemopoiesis apart from the myeloblastic proliferations generally followed the pattern of chronic myelogenous leukemia although the portal fields of the liver were less involved than the sinusoids The last case was anatomically one of panmyelosis myelofibrosis and osteosclerosis associated with reticuloendotheliosis but hematologically one of acute myeloblastic leukemia

Cases of panmyelosis have been reported under a variety of names but accurate differentiation from chronic myelogenous leukemia has not been enthusiastically pursued probably because of the uniformly ineffective therapy of the leukemias The etiology of the myeloses is obscure but there is evidence that in man benzene and radium may provoke a panmyelosis reaction Rabbit spleen eight days after x radiation is highly reminiscent of panmyelosis A similar reaction is sometimes

produced by metastatic tumors and other bone marrow replacements

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(5) Brit M J 2 411 414 A g 2 1953

neither had leukocytosis and both died of severe anemia after responding poorly to transfusions The five patients who were benefited had leukocytoses of 20 000 70 000/cu mm before treatment One with severe anemia and another with early osteosclerosis each had one course of x ray therapy to the spleen only abdominal discomfort was relieved and a sense of well being promoted The other three had several courses of treatment One patient with advanced myelosclerosis had good responses after two courses but died of severe anemia In this case x ray therapy seemed to diminish the degree of myelosclerosis as assessed by serial x ray pictures of the bones Another was greatly improved generally but treatment failed to affect the tendency to gastrointestinal hemorrhages The last patient derived great benefit for four courses each of which precipitated an attack of gout Subsequently treatment was less effective This patient died of general weakness wasting and gout

Patients with large numbers of circulating leukocytes with immature cells among them appear to do well on x ray therapy regardless of the degree of myelosclerosis Dosage should be just enough to relieve abdominal discomfort and general symptoms more than that may lead to leukopenia (seen in two patients) and anemia

Believing that the myeloid metaplasia of the spleen is secondary to fibrous and bony replacement of the marrow cavity some deem splenic irradiation harmful Others attribute the disease to changes in the undifferentiated cells of the bone marrow comparable to those causing increase of leukoblasts The reduction of the degree of myelosclerosis by irradiation of the bone in one case supports this view

Splenectomy though not done in these cases is advocated by some despite the discouraging reports of its results It may diminish the frequency of required transfusions

Report on 12 Cases of Giant Follicular Lymphoma (Brill Symmers Disease) Paul Chevallier Jean Bernard G Bilski Pasquier and D Christol[6] discuss the diagnostic and other problems of giant follicular lymphoma on the basis of these 12 cases recently observed by them The disease usually begins with gradual enlargement of one or two lymph nodes

(6) S g 4 665-699 1953

in the groin axilla or neck Onset is so insidious that the condition is frequently ignored by the patient in the beginning As the swellings increase and lymphatic involvement becomes more general splenomegaly may be added to the picture The patient s general condition however usually remains unimpaired until there is visceral and osseous extension Occasionally the order is reversed and splenomegaly appears as the first sign After some years unless spontaneous recovery occurs the possibility of which may be doubted death results from cachexia with a syndrome of lymphosarcomatosis

Differential diagnosis which requires elimination of various lymphoid conditions such as lymphoid leukemia and Hodgkin s disease is based chiefly on blood studies and biopsy of the spleen and lymph nodes roentgen investigation may also provide useful information in some cases

The cause of giant follicular lymphoma has never been definitely established and as a result the only treatment available is symptomatic In patients with splenomegaly as the initial and predominating symptom splenectomy gives excellent immediate results but even during the period of postoperative euphoria study of the blood picture reveals that the disease is progressing and sooner or later recurrent lymphatic involvement results in death Rapid recurrence is also usual after excision of enlarged lymph nodes Results of x ray treatment are often excellent as are also those obtained by intravenous injections of nitrogen mustard in certain cases in others however adequate doses cannot be given because of a drug reaction ACTH and cortisone have lately been tried with some success but a longer follow up is needed before their value can be accurately determined

[The diagnos s of this condition l ke that of all conditions associated with local or generalized hyperplasia of the lymphoid or reticuloendothelial apparatus in the absence of an altered blood picture can usually be made only by lymph node b opsy w th subsequent expe t pathologic interpretation —Ed]

Cutaneous Anergy and Hodgkin s Disease Because of the association of a negative tuberculin reaction and Hodgkin s di ease many attempts have been made to ascribe to the tubercle bacillus an etiologic role in this diesase However besides anergy to tuberculin these patients also have a lower

incidence of positive serologic reactions for syphilis fail to produce antibodies against brucellosis do not react to typhoid vaccination and have a diminished production of antibodies to pneumococcus polysaccharide Skin reactions to a variety of antigens are also frequently reduced

W Wilson Schier[7] (V A Hosp Brooklyn) studied reactions to cutaneous injections of antigens and histamine in 114 subjects 33 had Hodgkin s disease 17 had other systemic disorders and 64 were normal controls The antigens used which induced delayed responses were purified protein derivative (PPD) mumps virus extracts of Candida albicans and Trichophyton gypseum and normal allantoic fluid of chick embryo The reactions were read at 48 hours Reactions to injections of histamine phosphate (0 05 cc of 1 1 000 dilution) were read at 20 minutes

Histamine reactions were almost identical in controls and in the patients with Hodgkin s disease Normal allantoic fluid elicited only one reactor a control There were 86% reactors to mumps antigen among the controls and 18% among those with Hodgkin s disease Reactions to C albicans extract were obtained in 92% of the controls and 21% of the Hodgkin s disease group to T gypseum extracts in 72% of the controls and 27% of the Hodgkin s disease group and to PPD in 72% of the controls and 21% of the Hodgkin s disease group

Possibly important is the fact that 28 patients with Hodgkin s disease had been treated with cortisone nitrogen mustards or radiation There was however no correlation between the skin reactions observed and the therapy received or duration of the disease

Patients with several other forms of lymphoma were tested including chronic myeloid leukemia chronic lymphatic leukemia reticulum cell sarcoma lymphosarcoma and others Ten showed decreased reactivity though the lesions were slightly larger than those seen in the patients with Hodgkin s disease The patient with reticulum cell sarcoma was completely unreactive A history of clinical allergy was obtained in 11 controls and in 6 patients with Hodgkin s disease

The immunologic defect in Hodgkin s disease may be a failure to produce antibodies in normal quantities or there may be a lack of complement

(7) New England J Med 250 353 361 March 1954

↓ The next seven articles deal with various types of antileukemic therapy —Ed

Bone Marrow Changes in Patients with Chronic Leukemia Treated by Splenic X Irradiation Preliminary Report on 15 cases is made by F W Gunz[8] (Christchurch N Z Hosp) Sternal marrow aspirations were made in eight patients before the first and 24 hours after the last treatment of a full course of splenic irradiation Cellularity of the marrow showed no significant changes In five cases the number of immature myeloid cells decreased after treatment and in two there was an increase of the immature myeloid cells In one of the latter two no clinical response to irradiation was noted There was also an increase in the number of immature red cells in five cases this being the most striking change observed Either a fall in the number of immature myeloid cells or an increase in the immature red cells was seen in six of the eight cases These findings suggest that irradiation of the spleen indirectly produces variable changes in the marrow [or that the changes were within limits of spontaneous variation difference in site of puncture and in differential counts —Ed]

In six patients mitoses in the marrow cells were counted before the first and 24 hours after the last treatment but no significant changes were noted Since any effect on mitoses might be transient the marrow was also examined 80 minutes (the time of maximal irradiation effect) after the first treatment in 12 patients In 11 the number of mitoses was reduced in immature myeloid cells —to a significant degree in 6 patients who had had a large dose of x rays In some cases stray irradiation received over the site of marrow puncture was measured and the amount was so small as to preclude any possible effect of x rays locally on the marrow

In a control series of four patients with other diseases with one possible exception no significant changes were produced in the marrow by x radiation to other parts of the body

X rays directed to the spleen indirectly produce in the distant marrow temporary inhibition of mitoses of immature myeloid cells This may be observed only in leukemic patients or is perhaps a general effect of x ray administration

[A reasonable conclusion but one would like to know more about mal variations in repeated marrow punctures in the same patients without therapy —Ed]

(8) Blood 8 687 69 August 1953

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(7) New England J Med 250 353-361 March 1954

and the course showed a certain regularity Clinical symptoms and pathologic elements in the blood disappeared in the first week to be followed in the second and third weeks by a spontaneous improvement in the anemia Blood transfusions were not needed because of a strong increase in erythropoiesis granulocytopenia and thrombopenia disappeared in the blood and marrow Additional therapy included antibiotics vitamins B and C and salt poor diet

Side effects of cortisone included a reversible Cushingoid adiposity and slight increase in blood pressure Aminopterin produced a hemorrhagic diathesis due to disturbances in coagulation Cytologic peculiarities such as phagocytosis of erythroblast and erythrocyte in the bone marrow were seen during aminopterin and cortisone therapy and aminopterin caused a megaloblastic reaction and accumulation of basophilic pigment

The general inhibitory effect on bone marrow of aminopterin contrasts with cortisone s specific antianabolic action on the leukemia cell Inhibition of mitoses in blast cell anemias and in a premyelocytic form were observed The normalization of all cells of the marrow could be explained either as a modification of the metabolic equilibrium in favor of normal hemopoiesis or by a specific stimulation of the marrow In a mono myelocytic leukemia which did not respond to either cortisone or aminopterin a morphologic modification of the cells could be observed after every attempt at treatment Autopsy findings revealed atrophied adrenals only in children treated exclusively with cortisone

Triethylene Melamine in Treatment of Lymphomas and Other Neoplastic Diseases O Whitmore Burtner (Miami Fla) Louis C Jensen (Welch W Va) and John M Rumball[1] (Coral Gables Fla) observe that triethylene melamine (TEM) compared with nitrogen mustard has several advantages it is given orally thus avoiding the all too common venous thromboses and there is much less vomiting Having a relatively prolonged effect and being easy to give TEM therapy is well suited to the ambulant case and readily adaptable as maintenance therapy The drug acts much as nitrogen mustard in Hodgkin s disease and lymphosarcoma and is also of value in chronic lymphocytic leukemia Dosage must be

(1) A n I t Med 38 1222 1244 J 1953

Leukemia in Childhood Treated with Cortisone and Aminopterin C Gasser and R Cramer[9] (Zurich) evaluated their experiences with 15 of 25 leukemia patients hospitalized in 1951 52 The follow up period was sufficiently long that conclusions could be drawn

Cortisone caused a complete remission including a normalization of the marrow in eight patients with acute blast cell leukemia in one there were two complete successive remissions and in three others the remission was only partial



Fig 63—Total em on n p emy locyt le k m t e t d w th m pt rin aft p t tment w th e l ft bef m ss on r ght fte m s on (Courte y of Ga C nd C m R H l t p ed at acta 8 10 89 Ma ch 1953)

Cortisone was insufficient in two cases of premyelocytic leukemia with hiatus and two cases of myeloid leukemia without hiatus were aggravated by treatment Aminopterin was utilized only after treatment with cortisone and in alternation with it In a case of premyelocytic leukemia aminopterin used after cortisone caused a remission that was still in effect after 12 months (Fig 63) Cortisone alone was insufficient in this case In blast cell leukemias resistant to cortisone aminopterin caused one complete remission and many partial remissions

Myeloid leukemia without hiatus reacts to aminopterin but x ray therapy of the spleen has a greater effect Treatment should therefore be chosen on the basis of cytologic classification of the leukemia Since the introduction of cortisone the duration of survival in blast cell leukemia has been increased from 100 to 200 days

Remissions with cortisone were frequent and reproducible

(9) Hel t pa diat. cta 8 10 89 M h 1953

which leukopenia and anemia etc developed the marrow showed hypoplasia of the nucleated cells especially of megakaryocytes and increased numbers of degenerating cells

Gastrointestinal upsets were not serious but anorexia and nausea were present in most patients usually appearing 5 12 hours after a dose was taken Uremia as a complication of treatment was not seen

Triethylene Melamine in Treatment of Lymphomas and Leukemias is discussed by David A Karnofsky (Cornell Univ) This agent (TEM) which has been widely used in these diseases resembles nitrogen mustards (HN2) in that it delays death in leukemic mice and injures hemopoietic tissue and lymph nodes It is about 2 5 times as active by weight as HN2 and is less likely to cause nausea and vomiting

For intravenous administration the daily dose of TEM is 0 04 mg/kg (about 2 3 mg for the average adult) given for two to four days depending on hematologic and clinical status This corresponds to a daily dose of about 0 1 mg/kg HN2 TEM rarely produces venous thrombosis but if the solution extravasates a severe local reaction may develop Marrow depression is the limiting factor in dosage Intramuscular injection of TEM in a 1 2 mg/ml saline solution is well tolerated and the dosage is the same as for intravenous therapy

TEM is given chiefly by mouth As it reacts with organic substances in acid medium absorption varies and oral dosage requires close control The drug may be given with bicarbonate as enteric coated tablets or after an overnight fast The usual daily dose is 2 5 5 mg Oral therapy is well adapted to the ambulant patient Patients in poor general condition or with impaired marrow do not tolerate large doses and even those who have responded to an initial course should not be given the same dose during a second course as the marrow may have become susceptible Maintenance therapy is possible without marked effect on normal blood constituents The dose varies from 2 5 to 15 mg/month and is best given at two to four week intervals after ascertaining that no hematologic depression remains from the preceding dose

The drug is fairly well tolerated by mouth only 16% of patients having one or more episodes of nausea and vomiting These reactions can be diminished by restricting treatment to

( ) M Cl N rth Am 38 541 554 M h 1954

carefully gauged and adequate surveillance of the blood maintained to avoid bone marrow depression TEM therapy was given to 38 patients 7 of whom were outpatients throughout Bone and marrow studies preceded therapy and the blood was examined twice weekly in hospital patients and usually once a week in the outpatients In potentially sensitive patients a trial dose of 5 mg was given and the effect on the blood after one week noted before treatment was resumed Dosage varied with the patient s general condition previous responses to therapy bone marrow function etc and succeeding doses depended on the response elicited On occasion x rays were combined with TEM and transfusions antibiotics and so on used as indicated

Best results were obtained in the 14 cases of Hodgkin s disease The individual effect was related to the stage of the disease and the patient s general condition Sometimes improvement was incomplete and x ray therapy was given in addition The disease had been present an average of 48 months Improvement was usually noted after 9 days of treatment and lasted usually about 30 days Response was excellent in two patients good in seven and slight in five General symptoms were relieved in all

In lymphosarcoma TEM was ineffective in four cases of advanced reticulum cell type but was sometimes beneficial in three cases of the lymphocytic type and good in a case of follicular lymphosarcoma

Two of four patients with chonic lymphocytic leukemia gave a good and one an excellent response General symptoms improved spleen and liver diminished in size and blood and marrow lymphocytosis was reduced Here however marrow depression was a hazard a distinct tendency to thrombocytopenia and anemia being noted TEM is a useful adjunct to x ray therapy in this disease One patient with acute lymphatic leukemia had only temporary relief

Six patients with granulocytic leukemia acute and chronic showed varied responses Probably the existing therapeutic measures are optimal in the average case of these diseases Five patients with tumors not of the reticuloendothelial system were treated with no worthwhile palliative effect

Peak bone marrow depression occurred 12 50 days or longer after therapy was begun and was variable in nature Thrombocytopenia was late in some cases and in [illegible]

Myleran, New Cytostatic in Leukemias W Bollag[3] (Zurich) defines cytostatics as substances that exert a retarding effect on the growth of any tissue Myleran $CH_3SO\ (CH\ )_4$ OSO_2CH_3 showed in addition to its retarding effect on tumors a relatively selective retardation of myelopoiesis

The 12 patients in this study included 6 with chronic myeloid leukemia 2 with chronic myeloid leukemia in the terminal outpouring of myeloblasts and 1 each with acute myeloid leukemia chronic lymphatic leukemia multiple myeloma and seminoma Myleran was given orally in 2 mg tablets Most patients received 4 mg daily Two patients were temporarily given 6 mg daily When a remission was attained medication was either reduced or discontinued until a relapse

A daily administration of 4 mg of myleran for three to four weeks produced a general improvement in the patient s well being increase in appetite and weight gain Four patients could return to work within three months There was a definite reduction in the size of spleen and liver In two patients the number of leukocytes fell abruptly and in four there was a gradual drop In five patients there were remarkable changes in the neutrophil myelocytes and granulocytes according to their staining they appeared to lie between toxic and basophil granules The number of lymphocytes in the peripheral blood was not influenced In most patients the number of erythrocytes and the hemoglobin content rose

There were no side effects on the gastrointestinal tract the circulation or the skin One patient had pain in both arms and two became amenorrheic during therapy

From this and previous experience the author concluded that myleran is effective in the treatment of chronic myeloid leukemia In treatment of acute leukemia chronic lymphatic leukemia chronic myeloid leukemia during outpouring of myeloblasts multiple myeloma lymphogranuloma and other neoplastic diseases it was shown to be completely ineffective The retardation of increased myelopoiesis appears to be due to the antimitotic property of myleran

Effect of 1 4 Dimethanesulfonyloxybutane (GT-41 or Myleran) on Leukemia is reported by Nicholas L Petrakis Howard R Bierman Keith H Kelly Laurens P White and Michael B Shimkin[4] (Nat l Inst of Health) The disulfonic

(3) Schw m d W h h 83 87 876 S pt 12 1953
(4) C 7 383 390 M h 1954

alternate days They appear 4-12 hours after ingestion and are commoner in patients in poor condition

Marrow depression is similar to that seen with HN2 therapy platelet and leukocyte counts reaching the nadir at two to three weeks followed by prompt recovery With excessive doses of TEM platelets may fall to very low levels and hemorrhagic manifestations develop which may be severe and have been fatal If the patient survives for four weeks after the last dose of TEM and there is no underlying hematologic disorder recovery is assured Profound marrow depression is commoner with oral therapy and adequate hematologic surveillance is essential It is doubtful if TEM has any nephrotoxic action though hyperuricemia may follow rapid dissolution of tumor cells and may have some deleterious effect

In over 400 reported cases of Hodgkin s disease in which TEM was given 60 80% of the patients showed some clinical improvement the response lasting 4-20 weeks or longer Oral TEM therapy is most useful in the disseminated stage but patients may require concurrent x ray therapy later TEM is rarely helpful in the advanced disease Patients resistant to HN2 do not usually respond to TEM and vice versa

In lymphosarcoma and reticulum cell sarcoma TEM has been principally used in late stages and results have been poor In earlier stages it has caused regression of lymph nodes and clinical improvement

TEM has been fairly effective in chronic lymphatic leukemia and is indicated principally when the platelet count is not markedly depressed Complete remission is not produced in most cases but symptoms may be controlled for long periods by maintenance therapy TEM is ineffective in advanced cases In chronic myeloid leukemia in the early stages remissions may be regularly induced They usually last 6-12 weeks and can be prolonged by maintenance doses TEM is of little value in acute leukemias of adults and children It has been effective in polycythemia but comparison with radioactive phosphorus and x ray therapy will require study over longer periods

TEM has been of little value in mycosis fungoides and myelomatosis Trials in a variety of cancers showed that it has some activity in fibrosarcoma and carcinoma of the lung and ovary but more extensive studies are necessary to assess its therapeutic value

three cases during the rapid leukocyte decline and again three weeks after cessation of therapy No evidence of unusual hemopoiesis was noted but the more immature granulocytes of the marrow decreased during the first two weeks of therapy In one patient sections of marrow made both before and a month after treatment disclosed decreased cellularity and a return of both erythroid elements and marrow fat (Fig 64)



Fg 64—H t l g ect f bon m w f one p tient b f d on m th ft th p N t d ct f ll l ty d pp f m l f t p ft t eatment (Court y f P t ak N L. *t al* C 7 383 390 M h 1954)

No suggestion of a destructive process and no consistent or significant megakaryocytic abnormality were noted

Either transitory or no benefit was noted in the acute or monocytic leukemias and no effect whatever in either multiple myoma or carcinoma

Clinical Evaluation of New Antimetabolite 6-Mercaptopurine in Treatment of Leukemia and Allied Diseases is reported by J H Burchenal M L Murphy R R Ellison M P Sykes T C Tan L A Leone D A Karnofsky L F Craver H W Dargeon and C P Rhoads (New York City) There are qualitative differences in the ability of bacterial and mammalian tissues to use pre formed purines and pyrimidines therefore purine and pyrimidine antagonists may have a

(5) Blood 8 965 999 N mbe 1953

acid esters sharply inhibit growth of various transplanted animal tumors and are less toxic to bone marrow than the amine mustards One such compound—1 4 dimethanesulfonyloxybutane (GT 41)—depresses granulopoiesis in the rat and in man without appreciable effect on lymphopoiesis and has a favorable effect on chronic granulocytic leukemia Thrombocytopenia is considered its most important untoward effect A platelet count below 100 000/cu mm would be contraindicative Once the acute stage supervenes GT 41 is of little value

GT 41 was used to treat 21 patients 11 with chronic granulocytic leukemia 2 acute myeloblastic leukemia 1 unclassified stem cell leukemia 3 monocytic leukemia 2 multiple myeloma and 2 nasopharyngeal carcinoma Diagnoses were based on clinical and bone marrow studies Twice a week blood counts were made with marrow aspirations at 4 10 day intervals Initially the first course was 100 150 mg GT 41 over 4-6 days later 50-100 mg was given over 10 14 days and the maintenance dose was 6-20 mg/week

In chronic granulocytic leukemia objective and subjective clinical improvement was obtained with no evidence of toxicity Responses were characterized by well being decrease of liver and spleen size rise and maintenance of hemoglobin levels and fewer hemorrhagic symptoms Therapy repeated in eight patients resulted in complete or partial remission in five four of whom failed to respond to further therapy Of the eight three were alive 19 12 and 9 months after initial response the rest died 2 weeks to 4 months after the second course of therapy Resistance that developed in the terminal phase was related to the duration and severity of the disease Most patients because of previous x ray therapy were not regarded suited for further therapy Maintenance dosage was difficult to establish because of the great variation in individual requirements

GT 41 has a selective effect on granulocytes beginning slowly (7 10 days after therapy is begun) then abruptly producing a maximal fall in leukocytes at 17 20 days In most cases leukocytes then begin to multiply necessitating maintenance therapy Both mature and immature cells are affected but the immature cells are the first to diminish and also the first to rise again Transitory platelet depression was noted in

achieved temporary remission but the others failed to respond

In 35 patients with lymphomas and miscellaneous carcinomas and sarcomas 6MP caused no definite clinical improvement at doses which produced hematologic toxicity

The remissions obtained with 6MP were temporary with resulting resistance to the compound In some patients with acute leukemia on maintenance 6MP therapy the period of remission was somewhat shorter than that obtained with folic acid antagonists Consequently some of these patients were later treated with a methopterin A good hematologic and clinical response was noted in one patient There is no clinical or experimental evidence of cross resistance between these drugs thus 6MP may prove to be a useful adjunct to a methopterin therapy particularly in the initial treatment of leukemia Trials of combined therapy are now in progress

[Recent reports suggest that therapy with cortisone and a methopterin should be tried before 6-mercaptopurine However the latter adds another weapon to the therapeutic armamentarium against acute leukemia —Ed]

Plasma Cell Myeloma Gordon C Meacham[6] (Western Reserve Univ) studied 51 cases of plasma cell myeloma There were 29 males 42 patients were aged 50 or over All but 4 had anemia which proved to be macrocytic in 22 of 29 further examined and microcytic in 1 Plasma cells were present in the peripheral blood of 16 patients and were present in abnormal numbers in the 32 bone marrows examined in 30 cases accounting for 10% or more of the marrow cells No hemorrhagic phenomena were exhibited

In x ray studies of bones diffuse osteoporosis was a common finding (78 4%) and at times was the only bony lesion but it was more often associated with discrete osteolytic lesions In the 40 cases in which the tests were done total serum calcium content was above normal in 25% and alkaline phosphatase level was always normal

Serum globulin estimated in 49 cases was more than 4 Gm /100 ml in 30 and less than 3 Gm in 13 No relation to marrow plasmacytosis was observed but Bence Jones proteinuria was demonstrated in 3 of 23 patients with high globulin levels and in 9 of 13 with normal globulin levels

Renal insufficiency noted in 13 patients tended to be associated with low serum globulin level (6 of 13 cases) high

(6) A I t M d 38 1035 1047 M y 1953

chemotherapeutic effect on neoplastic disease because of a possible metabolic difference between normal and neoplastic tissues Of the compounds so far produced the most effective against transplanted mouse tumors is 6-mercaptopurine (6MP) Inhibitory studies on strains of Lactobacillus casei and Streptococcus faecalis show that 6MP operates differently from other antileukemic agents This is also suggested by the inhibition of strains of bacteria and mouse leukemia resistant to folic acid antagonists and by toxicity studies

Clinical trials were conducted on 107 patients with various neoplastic diseases The compound given in 50 mg tablets was well tolerated in doses of 2 5 mg /kg daily The maximum tolerated dose was given unless a therapeutic response occurred before this level was reached In leukemic patients improvement without ill effects was usual but in patients with other neoplasia toxicity appeared without therapeutic response Children tolerated 2 5 mg /kg easily and after four weeks the dose was usually doubled Sometimes a rapid fall in leukocyte count occurred after relatively small doses Toxic symptoms often appeared abruptly when the dosage was increased to 5 mg /kg in nonleukemic patients

Of 45 children with acute leukemia treated with 6MP 15 aged 2 12 had clinical and hematologic remission after 2 9 weeks which lasted 2 22 weeks Hematologic remission was judged present when the marrow count showed 30% or less stem cells plus lymphocytes Eight of these patients had had no previous therapy of the others four had failed to respond and one had become resistant to a methopterin Six had complete or partial hematologic remission on cortisone therapy Partial remission characterized hematologically by a marrow count of 30 70% stem cells plus lymphocytes was noted in 10 children aged 2 12 4 having had no previous treatment Five others had not responded or had become resistant to a methopterin Cortisone had produced complete remission in two and was ineffective in two

Of 18 adults with acute leukemia given 6MP only 12 had adequate trial 4 of these showed slight improvement and 8 did not respond

Nine adults with chronic leukemia including five with chronic and one with subacute granulocytic and three with chronic lymphocytic leukemia were treated The first five

pulmonary signs and pneumonic rales One week after improvement was secured with penicillin there was a recurrence with the same physical signs A febrile attack with pain in the side and rusty sputum was the first indication of myeloma in the third patient the pneumonic syndrome lasted for 40 days despite treatment with sulfonamides and later recurred with arthralgic manifestations Several similar successive disturbances were controlled with penicillin but death was finally hastened by a fresh pulmonary attack In the fourth patient relapsing pneumococcic septicemia localized in the lungs masked the underlying myeloma for several months Sternal marrow tests and radiographs showing extensive osseous destruction ultimately established the diagnosis of multiple myeloma but autopsy failed to disclose any myelomatous foci in the lungs which had the usual appearance of pulmonary congestion The infectious nature of the pulmonary complications—strongly suggested in all of the cases by the clinical course—was proved in this one by recovery of pneumococci from the blood

The repeated recurrence of pulmonary attacks in the last three cases suggests that the use of antibiotics may have allowed the recurrence by saving the patient s life in the initial episode In the past the pulmonary complications of multiple myeloma may often have caused death even before the existence of myeloma became known

[It is of great intere t that the serum ant body titer of such patients against a number of common antigens may be strikingly reduced —Ed]

Splenic Aspirations in Multiple Myeloma are discussed by Henry D Shapiro and R Janet Watson [8] This procedure has been used in over 150 cases of multiple myeloma at Kings County Hospital Brooklyn as an aid to diagnosis and study Whether multiple myeloma is primarily a skeletal disease or a disorder of the hemopoietic system is as yet unsettled The authors hoped to derive some information on the question from simultaneous marrow and spleen studies

Splenic aspirations were performed on 10 patients with multiple myeloma diagnosed on the basis of myeloma cells in the marrow x ray evidence of osteolytic or osteoporotic skeletal lesion anemia and high erythrocyte sedimentation rates In seven subjects because the spleen was not palpable splenic puncture was done intercostally into the area of maximal

(8) Bl od 8 755 759 A g 1953

ionized calcium (9 of 9 cases) and Bence Jones proteinuria (8 of 13 cases) It is possible that Bence Jones protein combines in the tubules with ionized calcium to form an obstructive cast with subsequent tubular damage

Sixteen autopsies were done in one of which nephrocalcinosis was found and in another amyloidosis The diagnosis of plasma cell myeloma was confirmed in each case

Treatment is unsatisfactory Temporary relief from pain was afforded by x ray therapy of bone lesions Urethane caused considerable symptomatic improvement but did not alter the duration of the disease Corticotropin has had encouraging reports in one case it caused striking improvement in hemolytic anemia and reduction of marrow plasma cells After four months pulmonary tuberculosis developed but hemolytic anemia did not recur

In 26 of 29 cases followed to completion the course was less than two years from onset to death

Infectious Pulmonary Complications in Course of Multiple Myeloma Four Personal Cases B Muller and M Berthouze[7] encountered such complications in four of seven patients with multiple myeloma treated in 1949 50 These pulmonary complications may be divided into those that reveal the presence of multiple myeloma and those that occur after the disease itself has been diagnosed The first type appears as a more or less acute pneumonic or congestive disturbance in the apparently healthy person or in one with slightly impaired general condition or vague discomfort Such complications precede development of the characteristic clinical picture by a longer or shorter period and often recur during the course of myeloma as acute or subacute attacks of pulmonary disturbance Complications of the second type taking the form of acute bronchitis or of genuine pulmonary congestion relapsing or not may be checked by the sulfonamides or penicillin They may sometimes even be discovered on auscultation without any functional evidence of their existence

In the first of the authors patients the pulmonary lesions which were terminal had little effect on the clinical picture producing only slight congestion at the base of the lung In the second patient with fully established myelomatous disease onset of the complication was abrupt with fever focal

(7) Sa g 4 257 65 1953

Electrophoretic Pattern in Multiple Myelomatosis Serum proteins from patients with multiple myelomatosis have been classified electrophoretically into three types type I those with increased gamma globulin fraction type II those with increased beta fractions or fractions lying between beta and gamma components (M fraction) type III those with ap

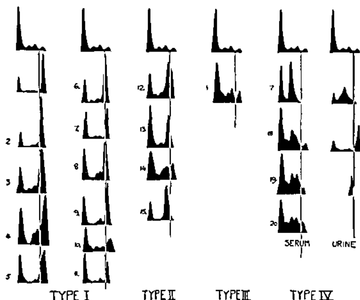
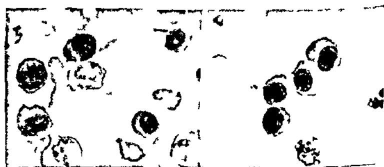


Fig 67—Elect ph t patt rn lcul ted f om filt p pe trip (Courtesy f Griffiths L L d B ew V A L, J Cl P th 6 187 189 A gu t 1953)

parently normal patterns Louis L Griffiths and V Anne L Brews[9] recorded results obtained by filter paper electrophoresis of serum proteins from 20 patients with multiple myelomatosis diagnosed by demonstration of myeloma cells by biopsy or at autopsy The patterns found including those of three urines were charted (Fig 67) Of the serums examined 11 were of type I 4 of type II and 1 of type III The four other serums possessed a globulin fraction which migrated between the albumin and beta fractions and which was called

(9) J Cl n P th 6 187 189 A gu t 1953

dulness to percussion the patient lying supine Palpable spleens were punctured just below the costal margin Smears were made of the aspirated material In nine patients myeloma cells were found in the spleen in the same order of frequency as in the marrow the proportion in the splenic material varying from 6 to 68% and in the marrow from 14 to 75% Although there was wide variation from patient to patient there was little difference between marrow and spleen of the same patient the greatest recorded being 26 5% myeloma cells in the spleen with 10 0% in the marrow The morphologic structure of the myeloma cells in the spleen and marrow in individual patients showed striking similarity (Figs 65 and 66)



F g 65 (l ft) —Myelom lls n bo e ma row
F g 66 (ght) —S m ase My l ma cells n splee
(C t y of Sh p H D d W tso R J Blo d 8 755 759 A gust 1953)

In normal subjects the average proportion of normal plasma cells does not exceed 3% The normal splenic differential count has been reported as plasma cells 0 2 3% neutrophils 8 25% band forms 1 7% lymphocytes 58-94% monocytes 1 2 2 4% and eosinophils 0 2 1 5%

The high degree of correlation between marrow and spleen findings militates against chance involvement and equally against the concept that extraosseous myeloma lesions are produced by direct extension of a skeletal tumor metastases or hematogenous implantation It rather suggests a simultaneous independent growth in the marrow and spleen which in turn implies that multiple myeloma is a generalized disease of the hemopoietic system [and so being freely admitted into the unpleasant company of leukemias and lymphomas —Ed]

Electrophoretic Pattern in Multiple Myelomatosis Serum proteins from patients with multiple myelomatosis have been classified electrophoretically into three types type I those with increased gamma globulin fraction type II those with increased beta fractions or fractions lying between beta and gamma components (M fraction) type III those with ap

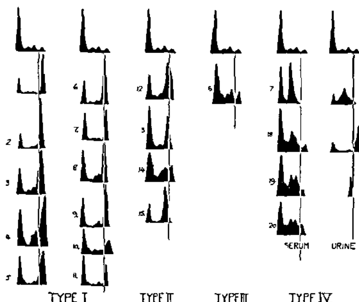


Fig 67.—Elect ph et p tt rn l l ted f m filter p p t p (Cou t y f Griffith L L d B w V A L J Cl P th 6 187 189 A gu t 1953)

parently normal patterns Louis L Griffiths and V Anne L Brews[9] recorded results obtained by filter paper electrophoresis of serum proteins from 20 patients with multiple myelomatosis diagnosed by demonstration of myeloma cells by biopsy or at autopsy The patterns found including those of three urines were charted (Fig 67) Of the serums examined 11 were of type I 4 of type II and 1 of type III The four other serums possessed a globulin fraction which migrated between the albumin and beta fractions and which was called

(9) J Cl n Path 6 187 189 A gu t 1953

type IV These serums had low total protein with decreased albumin and normal alpha 1 and beta fractions

Nine patients had proteinuria three (Cases 4 5 and 9) having traces of Bence Jones protein Three others (Cases 13 14 and 16) had a urinary protein similar in mobility to gamma globulin Three type IV patients had very small amounts of urinary protein of varied electrophoretic patterns

Flocculation tests including serum colloidal gold thymol turbidity thymol flocculation Kunkel and Popper tests were carried out on the serums of 13 patients with apparently dissociated results However when results were arranged within the four types of electrophoretic pattern most positive results fell into type I which was to be expected in view of the increased gamma globulin fraction of this group In type II in which the abnormal protein had migrated from the gamma position more normal results were recorded Within types III and IV results were normal It appears that the observed dissociation of the results of the flocculation tests is due to the fact that these tests were originally designed for detection of gamma globulins and the more an abnormal protein departs from similarity with the gamma fraction the less likely are these tests to yield a positive result

[It is interesting that H A Lawson has shown that irrespective of the gamma globulin pattern in multiple myeloma serum antibodies usually present are strikingly decreased or lacking This may relate to the reported frequency of pulmonary infections due to the pneumococcus in these patients —Ed]

Bone Marrow Plasmacytosis Review of 60 Cases Increased numbers of bone marrow plasma cells have been correlated by others with a variety of clinical disorders and with increased protein synthesis Employing a special method of evaluating the number and distribution of plasma cells in the marrow Herman Klein and Matthew Block[1] (Univ of Chicago) reviewed the relationship between bone marrow plasmacytosis plasma globulins and the associated clinical conditions

Technic —Clumps of cells aspirated from the sternum with an 8 gauge needle were fixed in Zenker s solution The tissue was embedded in nitrocellulose and sectioned and stained with hematoxylin and eosin azure The total number of plasma cells was graded 1 + to 4 + Plasma proteins were determined by the macro Kjeldahl method Any possible influence of recent therapeutic measures such as nitrogen mustard irradiation or P^3 was taken into account

(1) Blood 8 1034-1040 N mb 1953

Sternal biopsies of 60 cases previously reported as containing increased plasma cells were reviewed as unknowns together with randomly selected control specimens from 14 cases

Bone marrow plasmacytosis was most frequently associated with multiple myeloma (12) rheumatoid arthritis (8) hepatic cirrhosis (6) Hodgkin s disease (5) and granulomatous and collagen diseases (8) in the 60 patients Except for multiple myeloma in which complete marrow replacement by immature or mature plasma cells was frequent no single disease predisposed to a greater degree of plasmacytosis than another Hyperglobulinemia (above 3 Gm/100 ml) was present in 80% of the 60 cases whereas in the random group of 14 cases there were only 2 instances of hyperglobulinemia Some degree of correlation was noted between the degree of plasma cell proliferation and the more elevated globulin levels

Plasma cells were mostly seen surrounding arterial capillaries although random scattering clumping or complete marrow replacement occurred They were more resistant than most other marrow cells to irradiation and antitumor chemotherapy Bone marrow plasmacytosis has been reported by others as occurring in asthma hay fever cutaneous and febrile reactions to transfusions or drugs acute infections and rheumatic fever Its nonspecific nature is implied by its occurrence in neoplastic granulomatous infectious and allergic conditions At present there is little doubt that plasma cell proliferation is usually associated with elevated plasma globulin levels and it is a reasonable assumption that the hyperglobulinemia is derived from these cells •

HYPERSPLENISM

This medi ally popular term is used here to indicate that the spleen especially when enlarged as a result of a numbe of *different* disease processe eithe may exert some inhibitory influence on the bone marrow or may elect vely remove certain morphologic element from the ci culating bl od The discrimination of the spleen with respect to removal of d fferent sizes of red cell or starch gra ns is well established On the oth hand evidence for an influence of the spleen on the bone marrow n m n xtremely scanty but is added to by the observations reported n tl e fi st a t cle in this chapter —Ed

Incidence and Significance of Iron Containing Granules in Human Erythrocytes and Their Precursors A S Douglas and J V Dacie (Postgrad Med School London) found that

( ) J Cl P th 6 307 313 N mb 1953

iron staining inclusion bodies identical with those seen in red cells of the peripheral blood of postsplenectomy patients are normally present in marrow normoblasts during the process of hemoglobin formation

TECHNIC—A drop of marrow peripheral or splenic blood was placed on a slide and a film prepared and stained by the May Grunewald Giemsa method for demonstration of Pappenheimer inclusion bodies Other films were fixed in methyl alcohol for 10-20 minutes then stained for iron for 10 minutes with a freshly prepared mixture of equal parts of a 2% solution of potassium ferrocyanide and 2% hydrochloric acid preferably at 56 C The preparations were then washed and counterstained with 0 1% freshly prepared safranin Reticulocytes in fresh blood were stained in films made on slides prepared with cresyl blue then treated as above Safranin stains the reticulofilamentous material red and the iron containing granules appear blue against a pale red background

The commonest type of siderocyte contained a single or double granule usually near its periphery Twenty one observations of peripheral bloods showing numerous siderocytes indicated close correspondence between numbers of Pappenheimer inclusion bodies and siderocytes These cells were not found in the peripheral blood of normal persons or in significant numbers in conditions other than postsplenectomy conditions hemolytic anemias uremia or myelosclerosis The incidence of iron staining granules in reticulocytes was greater than in adult red cells Moreover iron containing granules (1 10 or more per cell) were present in 24 81% of the normoblasts of normal marrows Only in severe iron deficiency anemias were the marrow normoblasts free from such granules In these marrows extracorpuscular hemosiderin was always lacking but appeared with iron positive granules in the normoblasts after iron therapy Absence of these granules however did not necessarily accompany absence of extracorpuscular hemosiderin

Splenectomy especially if the underlying condition was a hemolytic anemia resulted in a considerable number of siderocytes and inclusion bodies in the red cells of the peripheral blood (table) Yet siderocytes were no more numerous in the splenic than in the peripheral blood at operation In postgastrectomy patients with megaloblastic anemia whose spleens had been removed treatment with vitamin B_{12} or folic acid diminished the number of siderocytes in the peripheral blood

The authors conclude that the iron in the normoblasts is

the precursor of the iron in the siderocytes and that in the siderocyte it with the basophilic staining material forms the Pappenheimer inclusion body Siderocytosis is probably a sign of cell immaturity normally the metabolism of iron in this form is nearly complete by the time the cell becomes a reticulocyte The increase in siderocytes in peripheral blood after splenectomy is not due to the loss of a filter for their removal but probably results from a slower maturation of the

INCIDENCE OF IRON CONTAINING GRANULES

	M o 10 O s VATIONS
% normoblasts in marrow with iron containing granules	53 8
% siderocytes	
in peripheral blood before splenectomy	2 4
in spleen blood*	2 0
in peripheral blood after splenectomy	15†

* Obta d by pl p tu n th p t t nd t pl tomy n
† M n t only p t ts

red cells so that they appear in the peripheral blood before the normal process of intracellular iron metabolism is finished Possibly the removal of this apparently humoral accelerating influence of the spleen on the metabolism of growing red cells is also responsible for the presence in peripheral blood after splenectomy of red cells containing nuclear material (Howell Jolly bodies)

[For information on the difficult but practical question of whether splenectomy will be clinically useful see the article by Loeb and his associates this YEAR BOOK page 279 as well as the two following articles here —Ed.]

Occurrence of Vascular Murmur over Greatly Enlarged Spleens is reported by Sven Erik Bjorkman[3] (Malmo Swe den) In 11 cases of splenomegaly due to leukoses polycy themia and other causes a faint systolic murmur was detected which was easily distinguished from a friction rub and ab dominal sounds It was only heard over greatly enlarged spleens with the lower pole at the umbilicus at least The murmur was of rather long duration (0 3 0 4 seconds) but not continuous it was heard evenly over the whole organ In eight cases phonocardiographic tracings were made and syn chrony with the heart beat confirmed The first and second heart sounds were registered over the spleen but showed a time lag when compared with a heart lead

(3) Acta m d d 145 79 83 1953

The splenic murmur is not a conducted cardiac murmur since it occurred in patients with and without cardiac murmurs In the former the splenic murmur was longer and of a higher pitch than that at the heart Further a definite thrill was felt over the spleen in some cases On the tracings the murmur began before the first heart sound appeared thus further supporting a splenic origin

In spleens examined pathologically no vascular abnormalities were found but when the spleen enlarges there is great dilatation of the sinuses which in effect amounts to aneurysmal distention of the vessels This may produce a murmur the audible sound being the summation of innumerable small noises each arising synchronously with the pulse Histologically these enlarged spleens show changes in the sinus walls which have been thought to bring about the increased filtration held to be the basis of hypersplenism The murmur may prove to be a useful bedside indication of hypersplenism

Chronic Neutropenia Report of Five Cases Treated by Splenectomy The study of chronic neutropenia is complicated by the overlapping of clinical features of various syndromes associated with leukopenia Correct diagnosis is important in selection of therapy Splenectomy appears to be curative in primary splenic neutropenia and beneficial in the neutropenia of splenic pancytopenia it may also be helpful in Felty s syndrome H Milton Rogers and Philip Dann[4] (St Petersburg Fla) treated chronic neutropenia in five patients by splenectomy with varying results

CASE 1 —Woman *72* with periodic cyclic neutropenia complained of fever and recurrent skin infections Leukocyte counts at various times for the past two years had been low Although she did not have splenomegaly leukocyte count improved and fever and infections disappeared after splenectomy Response was not so pronounced however as in splenomegaly ca es

CASE 2 —Woman 41 with splenic panhematopenia had 2 800 leukocytes 4 300 000 red cells and 73 000 platelets/cu mm hemoglobin content was 86" Liver biopsy and function tests disclosed no abnormality After splenectomy all elements formed in the marrow definitely improved and peripheral blood counts were always normal

CASE 3 —In man 62 with splenomegaly neutropenia and atrophic arthritis (Felty s syndrome) the leukocyte counts during several hospitalizations were low erythropoiesis and thrombocytopoiesis in the marrow were normal but with increase of myelocytic

(4) Am S g n 19 1071 1082 N mb 19 3

cells Histologic study of the removed spleen disclosed secondary amyloidosis Although leukocyte counts became normal he died of circulatory failure

CASE 4—Patient with previously reported neutropenia and Felty s syndrome died subsequently of carcinoma of the colon Autopsy disclosed metastases bronchopneumonia and portal cir rhosis with areas of liver cell necrosis and regeneration The Kupffer cells contained much yellow staining pigment Active erythropoiesis and myeloid development but reduced megakaryocyte count charac terized the bone marrow Evidence of tumor infiltration was lacking

CASE 5—Man 24 had neutropenia hookworm disease and hyperplastic bone marrow without splenomegaly After treatment for hookworm blood studies disclosed 4 300 000 red cells 1 500 3 800 leukocytes and 30 100 38 000 platelets/cu mm Histologic study of the spleen disclosed no increased phagocytosis Red cell count fell slowly to 2 040 000/cu mm other counts remaining the same Mar row studies disclosed depression of granulocytes good erythroid reaction and no megakaryocytes Biopsy of the upper tibia disclosed extreme marrow hypoplasia The anemia failed to respond to liver or vitamin B_1 therapy and the spleen which weighed 85 Gm was removed without benefit

Many difficulties are involved in the classification of neu tropenia (with or without splenomegaly arthritis or hyper plastic bone marrow) and in predicting the results of splenec tomy The presence of splenomegaly and hyperplastic marrow contribute to the expectation that a patient may benefit from splenectomy with patients who have severe splenomegaly benefiting most Splenectomy should always be considered in neutropenia with splenomegaly but the data should be care fully analyzed as the operation is not invariably curative

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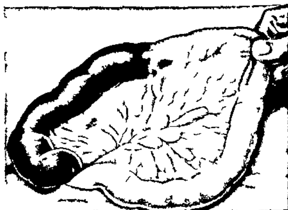
PURPURAS

Allergic Purpura Including Purpura Due to Foods Drugs and Infections is reviewed by J F Ackroyd (St Mary s Hosp Med School London) Basically purpura is due to vascular endothelial damage and thrombocytopenia though not an essential feature increases the hemorrhagic tendency Agents damaging vascular endothelium often affect the plate lets Therefore thrombocytopenia and capillary endothelial damage may have a common basis Allergic purpura is of two types (1) the Henoch Schonlein syndrome exanthem which

(5) Am J M d 14 605 63 M y 1953

is not of proved allergic origin though some foods have been held responsible (2) true purpura (with surrounding skin normal) probably due to an abnormal reaction to infection or drugs but rarely to foods

The Henoch Schonlein sydrome has three groups of symptoms—skin lesions gastrointestinal disturbances and joint pains It occurs most often in males commonly in children and adolescents and hemorrhage is rarely severe the purpura being often a minor component with visceral or joint pains predominating Clinical history varies and there is a



Fg 68 —H noch Sch le n y dr me D aw g of fi d g at op t o in boy 8 w th p rp h a d s gns f test al ob truct Ill d fi d m s w pal p bl mm d tely ab mb l us Le n fou d at l p tomy w b ro l tra vasat n of blood ffect ng bo t 4 ft of jej n m Th e w s n b t u t o N esect wa do d p t e t e ov r d (Co rte y of A k yd J F Am J Med. 14 605 632 May 1953 ed aw f m Ba l y H Brit J S g 18 34 1930)

remarkable tendency to recurrence A single attack seldom lasts more than a week and is usually succeeded by another after a few weeks or months Erythematous lesions resemble those of erythema exudativum multiforme rounded papules first appear on the extensor surfaces of the limbs buttocks and lower back and become purpuric within 24 hours sometimes forming hemorrhagic vesicles Joint symptoms usually affect the knees and ankles with periarticular swellings and effusions into the joints being rare Colicky abdominal pain is most striking and may be severe it is usually umbilical and radiating Vomiting often containing blood is frequent and occasionally an abdominal mass is felt which may lead to

diagnosis of acute abdominal obstruction At operation the lesion found is usually extravasation of blood or sero sanguineous fluid into the wall of the small intestine (Fig 68) sometimes with intussusception There is seldom more than mild anemia platelets are normal or only slightly reduced in number and hemostasis is normal Capillary fragility tests usually produce petechial hemorrhages and sometimes urti carial wheals

Histologically erythematous lesions are similar to those of erythema exudativum multiforme and endothelium of the small vessels may be normal or slightly swollen Clinical diag nosis is usually easy polyarteritis nodosa being excluded by skin biopsy Most cases clear up on symptomatic treatment Corticotropin therapy is equivocal in effect As nephritis is a serious complication patients should be treated in bed to min imize its incidence and severity

It is difficult to establish a relationship between purpura and infection The purpura probably depends on an abnormal susceptibility of the capillary endothelium to the infection which may also affect the platelets and produce thrombocyto penia This purpura varies from a few cutaneous hemorrhages to a fulminating purpura with extensive hemorrhages in the skin and bleeding from the mucosa In nonfatal cases there is no residual hemorrhagic tendency Hemorrhage is often severe enough to produce profound anemia and platelet count may be normal or slightly or greatly reduced No his tologic changes are seen in the vessels or in the spleen but a variety of morphologic changes has been reported in the megakaryocytes Treatment is symptomatic with transfusions if required Purpura appearing during convalescence is best explained as an allergic reaction similar to that of nephritis following streptococci infection

Purpura due to drugs has been reported but it is uncom mon and final proof lies in the effect of a test dose Purpura due to drug idiosyncrasy is a true noninflammatory purpura appearing suddenly a few hours or days after a single dose of the drug which may have been taken over long periods pre viously without ill effect There are anemia and thrombocyto penia Blood vessels are normal but marrow megakaryocytes may be normal reduced in number show slight morphologic abnormalities or exhibit maturation inhibition Diagnosis is

confirmed by testing the patient's blood in vitro with sedormid® or the suspected drug Treatment by withdrawal of the drug may be supplemented by transfusions and when heavy metallic substances are involved BAL

Sedormid® agglutinates and lyses platelets in fluid blood and during coagulation producing poor clot retraction and complement fixation Reduced complement titers after coagulation of blood in the presence of sedormid® can be demonstrated in sensitized patients There is apparently an anti

PLATELET LYSIS 0 + 0 + 0 0 0 0

COMPLEMENT TITRE

C S C S C S C S

N m l pl t l | Pla l t f m sed m d sens p t t | N mal pl tel t | Pl tel ts from sed rmid sen t p t

S m f m ed m d se p t t | No m l serum

Fig 69 —Platel t ly s d mplem nt fi at on by sedo m d® n sp s f pl telet from n mal p t t a d s do m d® nst t e p t t in h m logo a d hete ologo erum C = plat l t pen o serum d l ted w th s l S = pl telet s sp on rum d l t d w th a t t l t on f do m d® sal (C u tesy f A k yd J F Am J M d 14 605 63 M y 1953 f om P g t All gy ol 3 p 531 1952)

platelet factor in the serum of such patients as isolated normal platelets are lysed in sedormid® treated serums of sensitized patients but not in sedormid® treated serums of normal patients (Fig 69) This factor appears to be formed in response to a combination of sedormid® and platelets acting as a weak antigen Capillary lesions are probably produced in the same way the drug combining with endothelial cells to form an antigen Vascular and platelet lesions are due to antigen antibody reaction Athrombocytopenic purpura may be explained by the occurrence of only the vascular part of the process Patch tests may produce local purpura in the skin How far these findings apply in purpura due to other drugs is not known

Diagnosis of Sedormid® Purpura is discussed by D Kerr Grant[6] (Sydney) with reference to the use of patch and in vitro drug inhibition of clot retraction tests (Ackroyd) in six patients

CASE 1—Woman 29 who took sedormid® every night for seven months noted after two months that she bruised easily Dependent purpura appeared persisted and became worse 10 days before hospitalization Capillary fragility reaction was moderately positive a sedormid® patch test result negative and the platelet count 60 000/cu mm rising to 300 000/cu mm in one week One week later clot retraction in the presence of sedormid® was reduced by 16% During the next year she had mild recurrences of petechiae and bruising though she denied taking any more of the drug However all tests including platelet counts had normal results Twenty months after the first studies she was given a trial dose of the drug with no adverse effect on the platelets The test repeated later with higher dosage was also without effect

CASE 5—Woman 30 had taken 80 tablets of sedormid® irregularly over eight to nine months She then began taking 1 tablet every night and within a few days petechiae bruising and epistaxes appeared with hematuria and bright blood in the stools Platelets were scarce and clot retraction was reduced 50% in the presence of the drug A week later reaction to a patch test was negative and the platelet count 300 000/cu mm but clot retraction was still reduced 13% by the drug In two days this result also was negative During the next few months the platelet levels were sometimes slightly subnormal but other tests had negative results

CASE 6—Woman 69 over a year previously had taken sedormid® tablets irregularly Two or three days before hospitalization she took 1 tablet each night On the third day petechiae and bleeding of the tongue appeared followed by extension of the lesions with bruising all over the body The platelet count was 48 000/cu mm falling to 15 000/cu mm the next day Clot retraction was reduced by the drug 51% and 29% on consecutive days After a month clot retraction was still reduced though no more of the drug had been taken

These cases may not all represent sensitivity to sedormid® the diagnoses being mainly clinical and presumptive and results of specific tests frequently negative when performed some time after discontinuance of the drug The usefulness of the tests and test dosage probably depends on the length of time that the sensitivity to the drug persists If it persists long there is no need for haste otherwise in vitro tests should be performed as soon as presumptive diagnosis is made so that false negative results will be avoided

(6) B t M J 2 128 131 J ly 18 1953

Observations on Cases of Thrombocytopenic Purpura Due to Quinine, Sulfamethazine and Quinidine are presented by F G Bolton and R V Young[7] (Oxford England) with particular reference to in vitro platelet agglutination and lysis Results resemble those of Ackroyd who first demonstrated that addition of the drug to the plasma of patients recovering from sedormid® purpura caused agglutination and in the presence of complement lysis of patient s and normal platelets

CASE 1 —Girl 19 and healthy took quinine sulfate tablets irregularly One hour after taking a 5 gr tablet she had tinnitus fainted and on recovery noted petechiae and bleeding from throat and gums Physical examination in hospital disclosed hemorrhages and blood platelet count was below 10 000/cu mm Clinical recovery was rapid and platelet count was 207 000/cu mm 11 days later when she again took 2 quinine tablets with rapid reappearance of bleeding diathesis

CASE 2 —Man 50 who had received sulfamethazine for pneumonia two years before again received the drug 1 Gm every four hours After taking 7 Gm he noted a purpuric rash and had larger hemorrhages on hospitalization the next day Platelet count was 33 000/cu mm and rose to 118 000 almost a month later after a stormy hospital course with hematuria and melena requiring 12 blood transfusions

CASE 3 —Woman 63 occasionally took tablets of quinidine sulfate for palpitation the last a week before purpura appeared 10 days before she was seen by a physician Platelet count was then 31 000/cu mm and rose to 211 000/cu mm a week later

The effect of adding small quantities of the suspected drug to each patient s blood was studied For Case 1 about 5 ml heparinized blood obtained during remission was mixed with 0 05 ml of 0 14% quinine hydrochloride in saline Stained films demonstrated marked agglutination of platelets at 30 minutes with beginning lysis at 50 minutes increasing during the next 4 hours at room temperature For Case 2 0 1 ml of a 20% solution of sodium sulfamethazine in serum added to 10 ml venous blood caused pronounced platelet agglutination after 30 minutes and lysis beginning after 45 minutes For Case 3 0 05 ml saturated solution of quinidine sulfate in saline was mixed with about 5 ml heparinized blood Marked platelet agglutination occurred within one hour but this was not followed by platelet lysis No platelet agglutination occurred with quinine the stereoisomer of quinidine Control studies using normal blood samples with the same solutions

(7) J Cl n Path 6 320 3 3 N emb 1953

of the three drugs caused no platelet loss agglutination or lysis Heparinized plasma of Case 3 was centrifuged at high speed to yield platelet free plasma This plasma in the presence of quinidine sulfate caused agglutination of platelets in normal platelet rich plasma but no platelet lysis Without the patient s plasma the drug did not agglutinate the patient s or normal platelet suspensions After being stored frozen solid for more than two days patient s plasma lost its ability to agglutinate platelets in the presence of quinidine sulfate

In nine patients Ackroyd and others have shown platelet agglutination in vitro in presumptive drug induced thrombopenic purpura caused by recurrent use of sedormid ® quinidine or quinine presumably on the basis of sensitivity acquired by previous exposure to the drug Possibly such sensitivity may occur to drugs other than those already implicated by methods similar to those used by the authors Glassware employed in such investigations should be rendered water repellent

Idiopathic Thrombocytopenic Purpura A Challenge Mario Stefanini and William Dameshek[8] (Tufts College) review what is known about the disease Most theorists try to explain the relation of the low platelet count in idiopathic thrombocytopenic purpura (ITP) to normal or increased numbers of megakaryocytes and the varied response to splenectomy Some observers believe that megakaryocytes are not only increased in number but are grossly abnormal these changes have been regarded as possibly the effect of a splenic humoral agent since splenectomy produces striking improvement Others think that platelets are destroyed by the spleen A third group holds that thrombocytopenia is due to increased utilization of platelets at the periphery presumably to prevent hemorrhage from injured capillaries The spleen has been incriminated as inhibiting formation and release of platelets or as directly destroying them Splenic extracts from cases of ITP have been stated to contain substances depressing plat lets in animals and attempts have been made to show that normal spleen contains at least two principles regulating formation release and number of platelets

No theory explains all cases of ITP and analysis of case histories indicates that acute and chronic cases may be distinguished Acute ITP is of sudden onset often after some

(8) La t 2 209 212 A g 1 1953

infection or drug intake Capillary fragility and bleeding time are increased and hemorrhages are severe Later vascular resistance improves purpura decreases and the platelet count rises The disease usually has a self limited course of a few weeks to a few months The course of chronic ITP is pro longed and remittent capillary damage being minimal and bleeding less severe The platelets are abnormal in appearance and function but in some cases the count may be only slightly subnormal At splenectomy some cases reveal unsuspected splenic disease such as tuberculosis Lysis of platelets occurs in thrombocytopenic purpura due to sedormid* or quinidine In vitro studies indicate that this reaction requires in addition to platelets the presence of the drug complement and a serum fraction

Similarities of ITP to autoimmune hemolytic anemia have been stressed and these two diseases sometimes coexist Posi tive antiglobulin reactions have been reported and platelet agglutinins described Plasma of ITP patients can produce a fall in platelets in normal subjects this activity apparently being due to a globulin detectable in the plasma of splenecto mized patients with ITP Likewise a factor that causes rapid disappearance of normal transfused platelets can be demon strated in the blood of cases of ITP

Plasma from patients with acute disease does not induce severe thrombocytopenia in normal recipients and only seldom contains demonstrable platelet agglutinins but the rapidity of fall of injected normal platelets indicates some destructive agency Megakaryocytes are not greatly increased but show irregularities of nucleus and cytoplasm In such cases the immunologic mechanism is perhaps an allergy related to chemical viral or other agents Clinically and hematologically acute cases resemble those due to drug purpura

Treatment is hard to assess but splenectomy is not in variably successful in acute cases and corticotropin etc act favorably by control of vascular involvement rather than by an influence on platelets In chronic cases platelet agglutinins occur in 50% and perhaps in the others too in low concentra tion The spleen plays a minor role only probably disposing of platelets sensitized to the agglutinins Thus splenectomy affords relief until the reticuloendothelial system undertakes the work of the spleen In cases in which splenectomy causes

a lasting remission some splenic antimegakaryocytic sub stance must be postulated [A simpler explanation would be that removal of the spleen when it is an efficient filter for sensitized (agglutinated) platelets permits maintenance of an adequate platelet level According to Harrington splenectomy does not reduce the level of platelet agglutination factor in the plasma whereas spontaneous or cortisone induced remis sion does —Ed]

Platelets and their products are antigenic and toxins may modify their structure to permit autoimmunization Each case of ITP may well be an individual reaction syndrome and close observation is still required to help recognize any con stant associations

Thrombocythemia Report of Three Cases and Review of Literature are presented by Herbert Fanger Louis J Cella Jr and Henry Litchman[9] (Rhode Island Hosp Providence) In the study of myeloproliferative disorders few observations of high platelet counts and megakaryocytic hyperplasia have been recorded A moderate increase in platelet count is prob ably not uncommon and has been described in fractures operations anemias and dermatoses In thrombocythemia the platelet count is permanently elevated to three times normal values and there are megakaryocytic hyperplasia in the bone marrow and a tendency to venous thromboses and spontaneous hemorrhages

Case 1 —Woman 63 had a duodenal ulcer Blood examination showed 5 000 000 red cells/cu mm 15 Gm hemoglobin/100 cc. and 17 400 white cells/cu mm with 88% neutrophils Partial gastrectomy was done and the spleen removed because of enlarge ment Three years later she was hospitalized because of recurrent epistaxis and weakness Blood study showed moderate anemia and mild leukocytosis Platelet counts ranged from 3 800 000 to 4 400 000/cu mm bleeding time was prolonged and prothrombin activity was 70% of normal Results of all other tests were normal Marrow biopsy revealed megakaryo ytic hyperplasia The patient was given a transfusion and placed on liver and iron therapy She did well for about two years then died of bronchopneumonia The platelet count remained elevated at all times varving from 1,350 000 to 5,200 000

Case 2 —Man 37 during a routine physical check up was found to have thrombocythemia He bruised easily and had a pro- longed bleeding time The platelet count was 12 000 000/cu mm Bone marrow study showed megakarvocytic hyperplasia and there

(9) N w E gl d J Med 50 456 461 M 18 1954

infection or drug intake Capillary fragility and bleeding time are increased and hemorrhages are severe Later vascular resistance improves purpura decreases and the platelet count rises The disease usually has a self limited course of a few weeks to a few months The course of chronic ITP is prolonged and remittent capillary damage being minimal and bleeding less severe The platelets are abnormal in appearance and function but in some cases the count may be only slightly subnormal At splenectomy some cases reveal unsuspected splenic disease such as tuberculosis Lysis of platelets occurs in thrombocytopenic purpura due to sedormid[a] or quinidine In vitro studies indicate that this reaction requires in addition to platelets the presence of the drug complement and a serum fraction

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Therapeutic Evaluation of Corticotropin (ACTH) and Cortisone in 40 Cases of Idiopathic Thrombocytopenic Purpura was made by Louis R Limarzi and William R Best[1] (Chicago) The patients were aged 3 months to 69 years and 14 were males Twenty five cases were acute Pretherapy platelet counts in all subjects were less than 100 000/cu mm

Cortisone in four previously splenectomized patients produced lasting remission in one temporary remission in one and had no effect in two Of 12 given ACTH 5 had lasting and 6 had temporary remissions Of 11 on cortisone 2 had lasting and 4 had temporary remissions In 12 resistant cases both agent were given and 1 patient responded to ACTH temporarily but not to cortisone

Two lasting and six temporary remissions were produced in chronic cases Six lasting and five temporary remissions were produced in acute cases The nature and number of megakaryocytes bore no relation to the therapeutic response

Splenectomy in 13 unresponsive cases resulted in 7 lasting remissions 6 patients derived no benefit from this or subsequent hormonal treatment In nine patients with temporary remissions splenectomy produced lasting benefit in eight Preoperative hormonal therapy was followed by quite high postsplenectomy platelet counts Bleeding tendencies were occasionally improved without any increase in platelets Four deaths occurred three in acute cases

Use of ACTH in Preparing Patients with Idiopathic Thrombocytopenic Purpura for Splenectomy is described by Richard W Greene William W Faloon and Eugene L Lozner (State Univ of New York) Seven patients with idiopathic thrombocytopenic purpura were given ACTH or cortisone for periods deemed sufficient for the response to be noted before they were plenectomized Before and after therapy platelet and eosinophil counts were done and capillary fragility tests were carried out with use of a blood pressure cuff More than 15 petechiae to an area 2 5 cm in diameter was regarded as abnormal

CASE 1 —Woman 34 with a three month history of spontaneous bruising had numerous petechiae over arms and legs Platelet count was low and in the marrow there were increased numbers of meg k ıryc vtes With \CTH va cular fragility derreased but the

(1) P oc C t l Soc Cl R 6 65 66 1953
(2) Am J M S 226 203 213 A g t 1953

was x ray evidence of splenomegaly The patient has been followed for four years with no change in the findings

CASE 3—Man 67 hospitalized for intermittent claudication had mild anemia and a platelet count of 1 470 000/cu mm On the second day he became febrile incontinent and comatose and died. Autopsy revealed thrombosis with infarction of the right adrenal gland The marrow showed greatly increased numbers of mega karyocytes and megakaryoblasts There was no evidence of leukemia.

Of 28 reported cases (including the present 3) 8 were associated with myeloid leukemia and 6 with polycythemia These conditions were probably additional manifestations of myeloproliferation and not independent entities In two cases thrombocythemia was associated with carcinoma Tumor ne crosis may be a factor in such cases In a case associated with sarcoidosis there may have been splenic involvement with release of marrow from hormonal inhibition by the spleen A similar mechanism may have prevailed in two other cases occurring with splenic atrophy or after splenectomy Thus in most cases thrombocythemia would seem to be a secondary manifestation The existence of idiopathic thrombocythemia as an entity may well be questioned and in any case can be diagnosed only by exclusion Cases 2 and 3 reported here may be examples of the idiopathic disease

Idiopathic thrombocythemia is not a form of megakaryo cytic leukemia The tissues are not infiltrated by cells and there is no significant extramedullary platelet formation Idiopathic and secondary thrombocythemia affects chiefly adults Patients complain of fatigue and weakness and have a tendency to thromboses and hemorrhage Bleeding time may be prolonged and anemia is inconstantly present Platelets vary in size some reaching giant proportions with prominent granular centers Multinucleated cells like megakaryocytes are occasionally seen

There is also a poorly understood group of diseases in which there are thrombocythemia with large bizarre platelets mixed with megakaryocytes and granulocytes hepato spleno megaly extramedullary hemopoiesis and inconstant myeloid marrow hyperplasia Some consider cases of this type to be examples of atypical myelogenous leukemia

[Bigelow has shown that the vasotonic principle normally derived from platelets may be strikingly deficient in such patients despite the elevated platelet values—Ed]

Importance of the Disulfide (S S) Linkage in Blood Clotting Mechanism One approach to the problem of the basic mechanism by which the various clotting factors are chemically integrated has been the study of the specific reactive groups of the proteins involved particularly those containing sulfur Compounds containing sulfhydryl have been variously reported as inhibiting and accelerating clotting John R Carter and E D Warner[3] (State Univ of Iowa) studied the importance of the sulfhydryl disulfide groups in clotting reactions by introducing into a clotting system a variety of compounds known to block the action of these groups The system considered most suitable was a modified two stage prothrombin assay With this technic any inhibitory effect could be measured as a change in thrombin yield [See original article for details of technic —Ed]

Iodoacetate and iodoacetamide which transform SH groups into thioethers mapharsen® and p-chloromercuribenzoate which combine specifically with SH groups and ions of copper mercury and silver salts which also can combine with SH groups had no effect on the clotting mechanism Sulfhydryl compounds which specifically reduce the S S linkage to the SH form were represented by cysteine hydrochloride thioglycollic acid glutathione and BAL These had a pronounced inhibitory effect on clotting Sodium sulfite and oxidizing agents the latter consisting of potassium ferricyanide and hydrogen peroxide also inhibited clotting Thus reagents blocking S S linkages inhibit clotting whereas those inhibiting SH groups do not This inhibition could be reversed by suitable oxidation the degree of reversal varying with the inhibitory agent used and being almost complete in some cases This indicates that the bond between SH compounds and the clotting factor is not a strong one

When effective blocking reagents were incubated with the nonprothrombin clotting components which were then introduced into the prothrombin assay no inhibition of thrombin yield occurred Consequently these studies suggest that the presence of the disulfide linkage is essential for normal clotting of blood and that the effect of inhibitors can be explained by action on the prothrombin Previous workers have come to similar conclusions and one recent report describes the

(3) Am J Phy 1 173 109 114 Ap 1 1953

platelet count was unchanged After splenectomy there was a rise in platelets which was sustained for nine months with no purpura

CASE 3—Girl 13 with a three month history of petechiae and ecchymoses had a low platelet count and normal marrow ACTH induced a remission of vascular fragility and some improvement in the platelet count which fell when treatment was stopped She later responded to further dosage of ACTH and also to cortisone but the platelet count remained low After splenectomy a good hematologic and clinical remission occurred which had lasted for 17 months

CASE 4—Woman 37 with easy bruising since childhood and menorrhagia had several severe epistaxes and excessive postextraction hemorrhage Two weeks before hospitalization she became unconscious and was found to have subarachnoid hemorrhage She improved slowly Blood studies showed hypochromic anemia and low platelet count the marrow showing erythroid hyperplasia The tourniquet test result was borderline ACTH therapy yielded no platelet response and after splenectomy there was only slight temporary improvement in platelet count

CASE 6—Girl 15 with six month history of easy bruising had a positive tourniquet test reaction and blood studies revealed a severe hemolytic anemia of unknown origin and low platelet count The marrow showed erythroid hyperplasia the megakaryocytes being normal With cortisone and ACTH vascular fragility became normal and the platelet count rose but insignificantly After splenectomy platelet and red cell counts became normal and she remained symptom free

Splenectomies were performed without hemorrhagic complications and wound healing was unimpaired There was no correlation between hormonal therapy and results of splenectomy but the former always improved the vascular resistance The hemostatic defect of thrombocytopenic purpura is twofold platelet deficiency sometimes corrected by hormonal therapy and vascular fragility regularly improved by hormones

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COAGULATION DEFECTS

The abstracts in this section indicate the growing complexity of this field In many instances the reader will find it necessary to study the original article in order fully to comprehend them Fortunately for the clinician aside from hemophilia prothrombin deficiency and fibrinolysis appearing during surgical or obstetric conditions defects of blood coagulation are rare More precise identification requires highly specialized technics Transfusion of fresh blood is the most generally useful procedure The intravenous injection of fibrinogen can be life saving in emergencies associated with fibrinogenopenia —Ed

blood or from the tumor tissue Although considered unlikely no test for fibrinolysin was made

[This report is of great interest in view of the well known association of thrombosis of peripheral veins with carcinoma of the pancreas —Ed]

Differentiation of Hemophilia into Two Groups Study of 33 Cases J P Soulier and M J Larrieu[5] (Paris) attempted to evaluate a test for antihemophilic factor (AHF) which measures the effect of the unknown plasma on the recalcification time of a system containing hemophilic reagent prepared from hemophilic plasma and extracts of heated platelets Reexamination of known hemophiliacs was undertaken and the results indicated that in those tested two separate hemophilic factors A and B were present Plasma from a patient with hemophilia A acted as did normal plasma against reagent prepared from the plasma of a patient with hemophilia B and conversely

All 33 patients studied had typical clinical histories prolonged clotting time plasma recalcification time in presence of heparin greatly prolonged and serum prothrombin time very short at the fourth hour Twenty eight patients had hemophilia A Seven of them had mild clinical symptoms with normal or slightly subnormal clotting times but on test the AHF concentration was definitely hemophilic in each case One patient had a circulating anticoagulant and all had positive family histories Four patients had hemophilia B and all had severe symptoms Results of clotting studies were similar to those of the severe cases of hemophilia A Two patients had a circulating anticoagulant and two had positive family histories One patient had hemophilia of a mixed type designated AB

Hemophilia B has been previously reported under the names plasma thromboplastic component and Christmas disease It would seem that a few patients with hemophilia clinically indistinguishable from the classic disease have a deficiency in the plasma of a factor distinct from AHF in all cases the missing factor appears to be the same The designation hemophilia A and B is to be preferred because the heredity and clinical aspects of the two disorders are indistinguishable It can be extended to include deficiency of other factors which may be found within the hemophilia syndrome

(5) N w E gl d J Med 249 547 553 O tob 1953

inhibition of clotting by soy bean trypsin inhibitor as due to prothrombin inactivation Perhaps the soy bean acts by disrupting the disulfide linkage

Carcinoma of Body of Pancreas with Fibrin Thrombosis and Fibrinogenopenia is reported by Donald G McKay Hazel Mansell and Arthur T Hertig[4] (Harvard Med School)

Woman 56 had left infrascapular pain for two months She had been treated for anemia by liver extract There was no history of bleeding Complete x ray including barium studies of the alimentary canal and proctoscopy gave negative results Fecal occult blood was repeatedly detected There was moderate anemia with 3% reticulocytes but liver extract caused little response Laparotomy revealed tumor of body and tail of the pancreas with spread to liver and lymph nodes After operation a slight jaundice developed Prothrombin time was 22 seconds (normal 18 seconds) fibrinogen content 107 mg /100 ml (normal 200-400) and bleeding time 6 minutes Clotting time and platelet count were normal After discharge she bled profusely per rectum and eventually died in shock Autopsy showed the carcinoma to have spread widely In the heart long pendant friable vegetations were attached to the line of closure of three valves The liver contained many metastatic tumor nodules near which the central sinusoids of the normal parenchyma were filled by fibrin deposits none of which were seen distant from the tumor The portal vein contained a thrombus which was invaded by tumor Fibrin deposition was also seen in the spleen and in the arterioles of the rectal mucosa There was infarction of the rectal mucosa and spleen and a small gastric ulcer was found A thrombus was found in the right ovarian veins

Laboratory estimation of fibrinogen had not shown any marked decrease but it is likely that the fibrinogenopenia became more severe and led to massive hemorrhage and death The fibrinogenopenia may be explained by the widespread fibrin deposition the relation of which to the tumor tissue suggests diffusion of some substance Invasion of the blood vessels would allow the same substance to reach the spleen and heart Heart valve tissue response to fibrin was similar to that seen in acute rheumatism

Although a proteolytic enzyme trypsin acts as thromboplastin promoting clotting of oxalated plasma From this and other reports it would seem that cancer patients are prone to *hemorrhage* caused by fibrinolysins or fibrinogenopenia the latter following fibrin deposition or destruction of fibrinogen by a circulating fibrinolytic enzyme derived either from the

(4) C ce 6 862 869 S pt mbe 1953

More than one clotting factor may be defective Two brothers deficient in factor V (Ac globulin) were also deficient in factor VIII The prothrombin time was corrected with hemophilia A plasma but thromboplastin generation was unaffected The combined deficiency in factors V and VIII may be referred to as factor V deficiency with concomitant hemophilia A

Rarely partial correction of the clotting defect in hemophilia B may be found by mixing various samples In the two serums observed clot analysis suggests that an allelic form of hemophilia B cannot be assumed but rather that another clotting factor X is involved This factor has been demonstrated by matching experiments with serums from patients with hemophilia B and other hemorrhagic diathesis It decreases during dicumarol® therapy in avitaminosis K in hepatitis and in the newborn and slowly disappears on storage Mixtures of serum from such patients with the dicumarol® and hepatitis serums only partly corrects thromboplastin regeneration Deficiency of factors IX and X appears to be incomplete and in one case sex linked hereditary transmission seemed most probable Such cases may be regarded as examples of factor X deficiency (hemoglobin C?) and concomitant hemophilia B

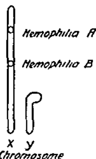


Fig 0—Loc t n f p th l g g tw f m f h m phil (Cou t y f K ll F Bl od 9 86 290 M h 1954)

Plasma Thromboplastin Component Deficiency I Studies on Its Inheritance and Therapy are reported by Martin C Rosenthal and Martin Sanders[7] (Mount Sinai Hosp New York City)

Boy 15 was hospitalized because of severe pain in the elbow and wrist for 16 hours He had a long history of easy bruising and hemorrhagic episodes necessitating over 60 hospital admissions Blood studies revealed slight anemia prolonged clotting time normal bleeding time and a high serum prothrombin activity Plasma transfusion gave prompt relief from pain and recovery was rapid There was a family history of hemorrhagic disturbances on the maternal side which was manifested only in males although the patient s

(7) Am J Med 16 153 16 J ry 1954

Factors A and B are present in normal and dicumarol* plasma Factor A disappears in oxalated plasma during stor age and during coagulation and is not adsorbed on barium sulfate or asbestos Factor B persists in stored oxalated plasma and in serum and is adsorbed on barium sulfate and asbestos Both factors are thermolabile Fibrinogen (Cohn fraction I) contains factor A only and is thus useful only in treatment of hemophilia A Blood and plasma transfusions are effective in hemophilia A B and AB

Symposium What Is Hemophilia? Is Hemophilia a Noso logic Entity? Until recently hemophilia was considered a well defined clinical entity involving a general bleeding tendency with emphasis on frequent joint bleeding skin hemorrhages, prolonged clotting time and sex linked hereditary transmis sion F Koller[6] (Univ of Zurich) encountered a family with mild hemorrhagic diathesis meeting all the criteria of hemo philia except that the clotting defect could be corrected by *typical hemophiliac plasma This suggested that sex linked* hemorrhagic diathesis might arise from lack of two different factors This differentiation was furthered by elaboration of the thromboplastin generation test which proved that one factor disappears during clotting whereas the other remains in the serum The first—antihemophilic globulin of Cohn—would be referred to as factor *VIII* and the second—the Christmas factor or PTC—would become factor IX the re *spective deficiencies would be referred to as hemophilias* A and B Since these diatheses cannot be distinguished clini cally the term hemophilia must necessarily apply to both In either instance the pathologic gene has to be located on the X chromosome (*Fig 70*)

Through modified thromboplastin generation test in 19 cases of hemophilia 10 were classified hemophilia A and 9 hemophilia B Two independent genes may be postulated since the same type of hemophilia appears to occur in each sepa rate family In the family with mild hemophilia the type was hemophilia A and in the typical hemophiliac whose blood was used in the tests the type was hemophilia B In the first not absence but rather a reduction of factor VIII was noted —in keeping with the concept that the mild gene is an allelic mutant at the same locus on the X chromosome as the classic hemophilia gene

(6) Blood 9 286-290 Ma h 1954

The term hemophilia should be abandoned and names used which indicate the specific factor lacking i e antihemophilic globulin deficiency plasma thromboplastin component deficiency and so on Confusing terms associated with hemophilia such as pseudohemophilia parahemophilia and hemophilia like diseases (circulating anticoagulants) are thus avoided If such designations are too wordy initials could be used as abbreviations

Effect of Antihemophilic Factor on One Stage Clotting Tests Presumptive Test for Hemophilia and Simple One Stage Antihemophilic Factor Assay Procedure are described by Robert D Langdell Robert H Wagner and Kenneth M Brinkhous[8] (Univ of North Carolina) Several tissue extracts and other materials were tested for thromboplastic activity with normal and hemophilic human and canine plasmas Normal and hemophilic plasmas had similar clotting times when crude concentrated tissue extracts were used as thromboplastin but with other materials (crude cephalin Russell *viper venom) the hemophilic plasma clotting time was pro* longed The latter materials were designated partial thromboplastins The partial thromboplastin clotting time of hemophilic plasma was much longer than that of normal plasma The antihemophilic factor (AHF) in normal plasma when added in small amounts to hemophilic plasma can restore the partial thromboplastin time to normal By comparing this effect in various plasmas against a known hemophilic plasma an assay of AHF content of the latter may be made The complete thromboplastic activity of crude extracts of hemophilic tissues is probably due to contamination with serum and other accelerators and not to small amounts of AHF

A presumptive test for the diagnosis of hemophilia consists of the determination of a prothrombin time and a partial thromboplastin time In hemophilia the first time is normal the latter prolonged

Assay of AHF activity in various plasma fractions showed the greatest activity in the fraction precipitated by one fourth saturation with ammonium sulfate For 12 normal plasmas AHF values were obtained by two different methods Although individual values corresponded well there was great variation between the various plasmas The plasmas of

(8) J L b & Clin M d. 41 637 647 Ap il 1953

mother had had spontaneous ecchymoses and postoperative bleeding and had a borderline prothrombin level Classic hemophilia was diagnosed but in testing the patient s blood against that of a known hemophiliac mutual correction of hemostatic defects was observed This prompted further study

Routine studies of the various clotting factors showed a striking similarity to those of a hemophiliac with prolonged clotting time prolonged plasma recalcification time and high serum prothrombin activity The serum prothrombin conversion accelerator was deficient in spontaneously clotted blood but normal when thromboplastin was added This occurrence however has been reported in cases of hemophilia Mixtures of the patient s plasma with that of true hemophilic plasma and plasma from a patient with plasma thromboplastin antecedent deficiency on recalcification showed mutual correction No such correction was seen with plasma from two patients with plasma thromboplastin component deficiency Plasma stored at 4 C for up to 19 days supplied the deficient clotting component thus indicating that it was stable This is in contrast with the known lability of antihemophilic globulin and factor V (labile) Equal therapeutic effects were obtained in vivo with fresh frozen plasma stored in the deep freeze seven day old plasma seven day old citrated serum and hemophilic plasma all stored at 4 C Clotting time was maintained at normal for about a week but the prothrombin consumption became abnormal in 72 hours The thromboplastin generation test showed that the peak of thromboplastin formation was delayed and never achieved normal values

Recent work clearly indicates the essential nature of plasma thromboplastin component Deficiency of this component produces a lag in thromboplastin formation which accounts for the prolonged coagulation and plasma recalcification times A decrease in the total amount formed is also manifest this fact being reflected in the poor conversion of prothrombin to thrombin Delay in production and poor yield of thromboplastin can also be demonstrated in hemophilia However the plasma thromboplastin component unlike antihemophilic globulin is present in serum and can be removed from plasma by barium sulfate together with prothrombin and serum prothrombin conversion accelerator Identification of the specific defect is important in that conventionally stored plasma may be used in treatment thus avoiding demands for fresh plasma

The mode of inheritance is virtually identical with that of hemophilia Even the mother s hemorrhagic tendency corresponds to the demonstrated low antihemophilic globulin concentration in asymptomatic female carriers of hemophilia

hours Normal serum and plasma had little effect but concentrated rabbit brain thromboplastin restored both clotting time and prothrombin consumption to normal The clotting defect did not respond to antihemophilic globulin in Cohn s fraction I or in fresh plasma Twenty one months after the onset of the disease the clotting mechanism was normal and the anticoagulant was no longer demonstrable in the blood

Studies on the patient s family showed no abnormalities except in the infant born during the disease In tests done during the first month of life there were abnormalities of the clotting time recalcification time and prothrombin consumption corresponding exactly with those of the mother In the blood abnormalities were minimal at 77 days and absent at 137 days thus proving temporary circulation of anticoagulant in the baby s blood There were no hemorrhagic symptoms

Similar clotting defects have been reported The transplacental transfer of the circulating anticoagulant recalls the transfer of immune bodies of measles and Rh sensitization A similar clinical and laboratory picture in much transfused hemophiliacs due to isoimmunization against antihemophilic globulin further supports the theory that an immunologic mechanism is at work No other types of antibodies or LE cells were detected

Effective therapy is precluded by such a clotting defect but the remission following sterilization invites speculation

Congenital Afibrinogenemia Paul G Frick and Irvine McQuarrie[1] (Univ of Minnesota Hosp) report a case of this rare condition

Boy 7 a known bleeder since birth received his first transfusion at age 5 days Later he had episodes of external hemorrhage which responded to transfusion and necessitated 16 admissions to the hospital He was admitted in April 1952 because of hematemesis melena and shock A transfusion was given at once during which blood clotting time was prolonged A few days later an abnormal thrombin titration and the small size of blood clot aroused suspicion of a defect in the last phase of coagulation Two weeks after transfusion the blood was found incoagulable and the presence of fibrinogen could not be demonstrated Plasma tested separately with equal volumes of calcium chloride calcium chloride and thromboplastin and bovine thrombin failed to produce a clot heated plasma showed no turbidity or flocculation between 53 and 56 C the plasma electro

(1) P d t 13 44-58 J y 1954

two normal persons were assayed for AHF on 10 occasions over 20 weeks When a control value of 72% was assigned for the plasma AHF of one, the comparative AHF values for the other varied between 107 and 134%

Negative results of presumptive tests for hemophilia were recorded in a family of known hemophiliacs in whom the AHF stood at 20% normal A positive result of the presumptive test has been obtained in prothrombin clotting time deficiency (a deficiency of a barium sulfate adsorbable clotting component) In hypoprothrombinemia the partial thromboplastin *time appears to be prolonged irrespective of AHF content* To exclude a mixed deficiency separate assays for each factor are essential

Hemophilia Like Disease Following Pregnancy, with Transplacental Transfer of an Acquired Circulating Anticoagulant, is described by Paul G Frick[9] (Univ of Minnesota Hosp)

In a woman 24 three months after a normal pregnancy hematomas of arm and leg developed suddenly and a therapeutic incision oozed blood for three weeks Extensive subcutaneous intramuscular and intra articular hemorrhages developed which multiple transfusions failed to control but after three months the disease remitted partially The patient again became pregnant She was well until two weeks before delivery one year after the first attack when extensive subcutaneous hemorrhages and hematuria suddenly developed The baby was delivered with little or no loss of blood but the next day profuse vaginal bleeding began and continued for 41 days requiring the transfusion of 89 units of blood and also some serum ACTH and stilbestrol were ineffective One week after the bleeding ceased she was sterilized by x rays She was hospitalized seven months later with suspected retroperitoneal bleeding the clotting time being *120 minutes Six months later she was symptom free*

At the height of the disease the clotting time was 130 minutes Failure to respond to transfusion suggested a circulating anticoagulant which was demonstrated by testing the effect of the patient s blood in vitro on normal blood Bleeding time platelet count clot retraction and Rumpel Leede reaction were normal thus excluding disorders of the platelets and capillaries Prothrombin time was normal and antithrombin tests including a protamine titration gave negative results Prothrombin consumption was minimal even over 20

(9) Blood 8 598 608 J ly 1953

case in the literature did the patient reach adulthood Fibrinogen is required not only for hemostasis but for defense and healing of infectious states

In previous reports family studies reveal a high incidence of parental intermarriage which with the frequent occurrence of hypofibrinogenemia in one or more relatives is suggestive of a recessive trait In this case the family study revealed no other bleeders but the parents were first cousins and were both hypofibrinogenemic Of the family one child the patient had afibrinogenemia two had hypofibrinogenemia and one was normal—the classic mendelian pattern of a recessive non sex linked character Of the 12 relatives examined 10 had hypofibrinogenemia

Severe Postoperative Hemorrhage Caused by Plasma Fibrinolysin Report of Case is presented by William A Steiger C J D Zarafonetis Dorothy Wilson and Clayton T Beecham (Temple Univ)

Woman 34 with menorrhagia and dysmenorrhea had pan hysterectomy surgery on one tube and both ovaries and appendectomy Toward the end of the operation blood began to ooze through out the pelvis a transfusion was started in view of the rather low preoperative hemoglobin level Then it was noted that all cut edges were bleeding Calcium gluconate koagamin® protamine vitamin K and nor epinephrine were given and almost continuous blood transfusion was maintained Bleeding continued the abdomen became distended and even injection sites oozed She died two days after operation In the surgical specimens adenomyosis of the uterus and endometriosis of the ovaries were found Autopsy revealed extensive multiple internal and external hemorrhages with widespread visceral petechiae

Blood removed shortly after the onset was incoagulable The typical findings associated with low ionized calcium were seen on ECG but calcium therapy was of no avail There was no spontaneous bleeding or increase of capillary fragility and the platelet count was normal Failure to respond to transfusions of fresh blood excluded hemophilia and absence of previous transfusions or pregnancy and a negative reaction to Coombs test made isoimmunization unlikely The fibrinogen content of the blood was less than 50% normal and the prothrombin time 27% normal A fibrinolysin was suspected and successfully demonstrated by lysis of normal blood clot.

Profibrinolysin a fibrinolysin precursor exists in the globulin plasma fraction and since it may be activated by emotional stimuli epinephrine etc an increase in the fibrinolysin titer of the blood is probably part of an alarm reaction

(2) Ob & Gy 2 99 104 J ly 1953

phoretic pattern showed no fibrinogen peak and was identical with the pattern obtained for serum The patient s plasma was repeatedly assayed for fibrinolytic or fibrinogenolytic activity without success Platelet counts were consistently normal and prothrombin assay by the two stage method was normal (360 units/ml) There was normal concentration of antihemophilic globulin and prothrombin conversion factors labile and stable the latter being tested against serum from a patient with congenital deficiency of stable factor Prothrombin consumption was more rapid than normal probably because there was no fibrin to interfere with the action of thrombin on the conversion of prothrombin Plasma thromboplastic component was shown to be pre ent by testing the plasma on a patient with a deficiency of this component About 4 Gm of fraction I was transfused and fibrinogen levels were observed at intervals The value obtained 30 minutes after injection 161 mg /100 cc. corresponded to half the normal concentration There was a gradual fall to zero during 12 days Comparison with previous reports is difficult and this period seems rather short but studies of citrated plasma transfusions substantiated the results The patient s plasma fibrinogen free with all the clotting factors in normal proportion was diluted with normal plasma to study the effect of fibrinogen concentration on the prothrombin time and on the clotting time with thrombin Fibrinogen concentration has to fall appreciably to level below 200 mg /100 cc before a moderate prolongation of these tim s is observed but below 50 mg the times increase rapidly

X ray examination revealed a duodenal ulcer which healed with two months of dietary treatment and repeated transfusions of blood and plasma (fibrinogen being required for healing as well as for hemostasis) Numerous liver function tests were negative The serum cholinesterase was raised but this was of doubtful significance

In afibrinogenemia hemorrhage occurs early in life but otherwise symptoms are not so severe as in hemophilia and hemarthrosis does not occur Laboratory tests show indefinitely prolonged clotting and prothrombin times in the presence of a normal bleeding time and platelet count negative cuff test and absence of clot retraction It is doubtful that the reported occasional occurrence of temporary thrombocytopenia is an essential part of the disease Increased capillary fragility which occurs rarely is probably a reflection of the thrombocytopenia Bleeding time especially in children is variable

Treatment during acute bleeding consists of transfusion with pla ma and whole blood and ideally the fibrinogen concentration should subsequently be kept above 50 mg /100 cc Plasma for therapeutic purposes need not be fresh as fibrinogen stores well Prognosis is poor and in only one reported

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(2) Ob t & Gy 99 104 J ly 1953

The uterus and lung are rich in fibrinolysin and precursors Severe capillary bleeding following fibrinolysis has been reported in a variety of operative procedures and the presence of malignant tissue seems to predispose to it Shock and anoxia are not necessary for activating the lytic system Diagnosis is easy but treatment is difficult Cortisone remains to be more fully evaluated but intravenous administration of 2 or 3 Gm fibrinogen is probably the treatment of choice

[Fibrinolysis is most likely to develop in patients with premature separation of the placenta or retained dead fetus It also may occur in surgical procedures especially when prolonged and accompanied by blood loss *A fibrolysin of prostatic origin has also been reported in metastatic* disease of that organ —Ed]

Congenital Hemorrhagic Syndrome Due to Deficiency of Coagulation Factor Recently Isolated under Name of Factor VII, Convertine, S P C A (Congenital Hemorrhagiparous Hypoconvertinemia), was found in an infant by J L Beaumont and Jean Bernard[3]

Infant after normal delivery weighed 3 500 Gm at birth The first hemorrhages appearing on the lips on the 4th day of life were followed by generalized ecchymoses and petechiae Profuse repeated rectal and umbilical hemorrhages began on the 6th night and continued uncontrolled for several days Daily transfusions and vitamin K therapy finally resulted in improvement but nine days after its discontinuance on the 22d day of life fresh hemorrhages had to be checked by transfusion Repeated hemorrhages during succeeding weeks were always stopped immediately but transiently by transfusion of 20 60 Gm fresh blood given 20 times between March 15th (the day of birth) and June 24th The parents were both healthy and had normal bleeding coagulation and prothrombin (Quick) times At first count the child s bleeding time was 8 minutes the coagulation time 20 minutes and clot retraction normal The prothrombin time (38 seconds six hours after the first transfusion) rose to 68 seconds and remained at or above this rate in blood drawn at least 24 hours after transfusion

Analysis of the coagulation process led to the detection of the disorder responsible for the syndrome The essential anomaly—permanent prolongation of Quick time—was traced to deficiency of a normal plasma and especially serum factor that remained almost unchanged after the plasma or the serum had been kept for 20 days or heated to 37 C it was *absorbed* by $BaSO_4$ and absent both from beef plasma filtered through a 20% asbestos *Seitz filter and from plasma treated with dicu*marol with a Quick time of 103 seconds This factor is not

(3) Acta m d sc nd 145 00 215 1953

prothrombin but rather one that is necessary in the rapid conversion of prothrombin into thrombin It was possible to correct the defect in prothrombin consumption by the addition of increasing concentrations of normal (aged) serum to the plasma before coagulation when the concentration was 4 100 the prothrombin remaining in the serum dropped to 6% one hour after clotting After transfusion of 30 Gm fresh blood prothrombin time (Quick) returned to normal for about four hours Thereafter it rose progressively until within 24 hours it had attained approximately its original level

Two factors necessary to the rapid conversion of prothrombin into thrombin can now be recognized Quick s labile factor (known also as Ac globulin factor V and accelerin) and convertine (S P C A cothromboplastin or factor VII) Study of the patient s plasma congenitally deprived of convertine proved that some of this factor is necessary to rapid prothrombin conversion and normal prothrombin consumption Pure hypoconvertinemia is rare The authors found only one case in a girl 4 treated by Alexander and co workers The findings in that case and in the one now reported are similar both were characterized by congenital deficiency of a serum coagulation factor that has the properties of convertine The authors call this syndrome congenital hemorrhagiparous hypoconvertinemia

Primary and Secondary Purpura Hyperglobulinemia is discussed by Horst Dorken[4] (Univ Clinic Hamburg Eppendorf)

CASE I—Woman 50 had fleeting swelling of the large joints accompanied by small petechiae on legs and forearms for 20 years As attacks subsided the petechiae turned into brownish pigmentation The appearance of petechiae was precipitated by heat light and physical exercise On hospitalization after an attack of purpura examination revealed on both legs up to the inguinal region several erythematous pea sized lesions some of them hemorrhagic coalescing in areas to dime size A small hemorrhage was also seen in the urethra and the vaginal introitus Hemoglobin content was 66% red cells 3 600 000 white cells 2 100 sedimentation rate 89/116 Biopsy revealed normal bone marrow Bleeding clotting and prothrombin times were normal Total protein was 8 85 Gm /100 ml thymol turbidity 34 units Electrophoretic values were albumin 39% alpha globulin 7 6% beta globulin 11 4% gamma globulin 42% No foci of infection were found

(4) Art h m t 10 340 349 D mbe 1953

CASE 2—Man 42 had had several attacks of polyarthritis from 1937 to 1948 and mild jaundice in 1942 From 1950 he had several attacks of purpura first on the legs later on the thighs Examination in 1952 revealed moderate enlargement of the liver with slight increase in serum bilirubin values Total protein was 8 2 Gm /100 ml with 32% gamma globulin Sedimentation rate was somewhat elevated

The syndrome of purpura with hyperglobulinemia as described first by Waldenstrom is characterized by benign recurring purpura accompanied by moderate hypoproteinemia and great increase in gamma globulin elevated sedimentation rate and positive results of serum flocculation and turbidity tests In primary purpura hyperglobulinemia no other systemic disease is found whereas in the secondary type other organs may be involved as in Case 2 in which the purpura was thought to be related to liver damage following hepatitis

The course of the primary type is benign Remissions or cures have not been described *Pathogenesis is unknown* No successful treatment has been found Differential diagnosis should exclude plasmacytoma the leukemias and chronic kidney liver and infectious diseases

Hyperglobulinemia as Cause of Hemophilia Like Disease Inga M Nilsson and Anders Wenckert[5] (Malmo Sweden) report a case of probable familial hyperglobulinemia in a woman with a circulating anticoagulant antagonistic to the initial phase of coagulation most likely to the antihemophilic globulin

Woman 44 had a history extending over a long period of fatigue headaches bilateral pleurisy transient joint pains deep subcutaneous and muscular hematomas and severe hemorrhage after trauma Hyperglobulinemia an elevated sedimentation rate and a prolonged coagulation time had been demonstrated Present examination revealed large hematomas on the arms and legs The liver and spleen were not palpable and the rest of the examination revealed no abnormalities There was a family history of a protein disturbance with hemorrhages in a sister

The patient had normochromic anemia with 63 70% hemoglobin and a normal white blood cell count Total protein was 8 9 Gm /100 ml with 5 8-6 5 Gm globulin 1 6 3 3 Gm albumin and 0 3 0 37 Gm fibrinogen The sedimentation rate was 100 mm /hour when tested on oxalated or citrated plasma There was no sedimentation of the red blood corpuscles in native blood kept in iced silicone-coated centrifuge tubes until after several hours simultaneously with the appearance of the first fibrin threads The red blood corpuscles then

(5) Blood 8 1067 1077 Dec mb 1953

descended rapidly for 15 minutes and a clot formed The thrombocyte count was 130 000 200 000 serum calcium level 10 6 mg /100 ml bleeding time three to four minutes tourniquet test negative fibrinogen normal and prothrombin about 80% Prothrombin consumption was greatly lowered Coagulation time at room temperature and at 37 C was 25 50 minutes and 60 120 minutes on two occasions There was a slow and initially incomplete formation o the clot as only part of the fibrinogen was transformed to fibrin For several hours after the first signs ot coagulation appeared formation of new fibrin threads was noted No signs of clot retraction could be observed until after four to six hours Addition of sufficient amounts of thrombin to the patient s plasma caused normal fibrin formation and clot retraction When the patient s oxalated plasma or serum was pipetted in advance in coagulation tubes and normal blood added directly from the venipuncture the patient s plasma or serum lengthened the clotting time of normal blood

Experiments were carried out to isolate the anticoagulant factor and determine its chemical characteristics When the plasma proteins were precipitated the prolonging effect could no longer be demonstrated The anticoagulant substance could therefore be assumed to consist of a protein or to be associated with such a compound The plasma and serum protein components were separated by salting out with ammonium sulfate and by paper electrophoresis The patient s anticoagulant factor was found in the gamma globulin fraction The lengthening factor could be destroyed by incubating trypsin with the globulin fraction The anticoagulant factor was not dialyzable It retained its activity when heated to 56 C for 30 minutes but was destroyed at 70 C The factor showed only slight reduction in activity after prolonged storage It was not adsorbed by barium sulfate and tricalcium phosphate and was still active after Seitz filtration of the plasma

In at least five of the previously reported cases of this sort abnormal plasma proteins were observed which as here probably combine with and *inhibit the action of the normal* antihemophilic globulin In other cases of hemophilia like disease the cause has been assumed to be an isoimmunization process caused by pregnancy or by repeated blood transfusions This patient a nullipara had never received a blood transfusion

THE HEART *and* BLOOD VESSELS *and* THE KIDNEY

TINSLEY R. HARRISON M.D

PART IV

THE HEART AND BLOOD VESSELS AND THE KIDNEY

CONGENITAL HEART DISEASE

Role of Auscultation in Diagnosis of Congenital Heart Disease Phonocardiographic Study of Children. John D L Reinhold and Alexander S Nadas[1] (Harvard Med School) present a phonocardiographic study of 64 patients with congenital heart disease in order to demonstrate accurately the auscultatory phenomena detectable with the stethoscope The first heart sound complex is made up of four components including two valvular sounds—auriculoventricular (A V) valve closure and semilunar valve opening The second sound complex likewise has two valvular components The A V valve opening is generally inaudible but closure of the semilunar valves is well heard and may be split with asynchronous closing of the aortic valve followed by closing of the pulmonary valve

The A V component of the first sound was frequently accentuated in patients with right ventricular hypertension and was usually best heard at the apex or the second and fourth left intercostal space The semilunar component was exaggerated at the second right interspace in patients with aortic stenosis The pulmonary element of the semilunar opening was diminished or absent in most patients with severe pulmonic stenosis

The greatest degree of splitting of the semilunar component of the second sound was observed in patients with atrial septal defects and right bundle branch block Patients with pulmonic stenosis of all varieties had either a single semilunar component or only a mild degree of splitting this was also noted in patients with aortic stenosis The intensity of the second sound particularly its semilunar component was greater in the second left than the second right interspace in normal children and in most of those with atrial defects small ventricular defe ts and patent ductus arteriosus There is an exaggeration

(1) Am Heart J 47 405-423 M h 1954

The intercostal and bronchial arteries arising just distal to the stricture almost invariably were greatly enlarged thin walled and extremely friable The degree of vascular damage to the aorta itself in the vicinity of the stricture was related directly to the duration of the lesion The evidence suggests that males more than females are likely to undergo severe vascular damage

Postural Effects in Tetralogy of Fallot Most speculation about the mechanism of postural effects in tetralogy has centered on the idea of a fall in systemic blood pressure which causes an increase in venoarterial shunt This concept however is open to question because clinically these patients do not seem to be suffering from acute arterial hypotension Paul Lurie[3] (Indiana Univ) observes that the favorable postures are those which tend to minimize the effect of gravity on venous return by compressing the venous reservoirs of the abdomen and lower extremities and/or bringing them toward heart level Unfavorable postures (quiet standing especially after exercise) permit blood to be pooled farther from the heart in regions where more work must be done to return it Arterial oxygen saturation was measured in 10 patients with tetralogy of Fallot while they were standing quietly There was a 7 34% decrease In another experiment a 15% decrease in oxygen saturation which occurs with quiet standing could be reversed by squatting Application of elastic bandages to the legs to compress venous channels significantly lessened the decline in arterial saturation during standing Pulmonary artery and brachial artery catheterization in one patient demonstrated fall in systemic flow as a tilt table was elevated toward the vertical There was no change in calculated venoarterial shunt nor was there arterial hypotension

Lurie believes that postures which reduce venous return while systemic oxygen extraction is maintained cause returning venous blood to contain a lower oxygen concentration This less saturated venous blood mixing with saturated pulmonary venous blood yields a resulting arterial mixture of lower saturation The untoward effects of such postures are manifestations of hypoxia

Diagnosis should not be based on a history of squatting but if possible on a simple test of leg exercise to the limit of tolerance Ask the child to remain standing and observe

(3) Am J Med 15 97 3(6 September 1953

of this relationship in the presence of lesions producing pulmonary artery hypertension and a reversal of the finding in patients with pulmonary stenosis

Systolic murmurs due to stenosis were heard in a diamond configuration and when due to aortic or pulmonary lesions were well transmitted to the neck Plateau or decrescendo systolic murmurs were registered in patients with septal defects Children with large left to right shunts commonly had a variety of diastolic murmurs

Anatomic Variations and Pathologic Changes in Coarctation of the Aorta Study of 124 Cases O Theron Clagett John W Kirklin and Jesse E Edwards[2] (Mayo Clinic) point out that the chief considerations in the clinical and surgical aspects of coarctation of the aorta are (1) the relative position of the coarctation—whether proximal or distal to the ductus arteriosus and (2) the patency of the ductus four types are thereby delineated This classification may be further modified preoperatively through observation that hypertension in the right arm with feeble left arm pulses may result from atresia or stenosis of the left subclavian artery or coarctation proximal to that artery or that hypertension in the left arm with feeble pulses in the right may be caused by stenosis of the right subclavian artery or by the origin of the right subclavian artery as the fourth branch of the aorta at a point beyond the coarctation

The aortic wall at the site of coarctation has a curtain like infolding of the media involving the superior anterior and posterior aspects of the aorta The lower portion of the aortic wall or that portion into which the ductus inserts does not take part in the deformity The external diameter of the aorta although narrow is considerably wider than the diameter of the lumen In most of the cases studied the diameter of the aortic lumen did not exceed 2 mm Sometimes it was entirely closed In four cases the stricture was proximal to the origin of the left subclavian artery and in two it was exactly at the origin of that vessel which was an obliterated fibrous cord Generally it was 0 5 2 cm distal to the origin of the left subclavian artery The ductus arteriosus was patent in 16 of the authors cases It was not considered a contraindication to resection and repair of the coarctation

(2) S g Gy & Ob t 98 103 114 J n y 1954

20 the oldest was 56 In 15 reported cases there was pulmonary atresia and some form of pulmonary obstruction—usually valvular stenosis—was present in 24 others In general the patients with pulmonary stenosis without atresia survived considerably longer than those with no obstruction in the pulmonary artery Abnormalities of the atrial septum were common it was absent in 27 of the 74 hearts examined these were examples of cor biloculare An intact atrial septum was present in 9 patients and some degree of patency in 30 In most cases there was transposition of the aorta and pulmonary trunk A rudimentary ventricular chamber was noted in about a third of the cases It was thought to be a remnant of the bulbus cordis and not a second ventricle This chamber is generally anterior and since there usually is transposition of the great vessels the vessel arising from this chamber is most frequently the aorta The chamber beyond an infundibular stenosis is also a remnant of the bulbus cordis

Since there is a better prognosis when pulmonary stenosis is present no attempt should be made to relieve it unless cyanosis is severe and the disability calls for it In such circumstances a subclavian pulmonary anastomosis may improve the condition

Cyanotic Heart Disease with Continuous Murmur Basing his study on three cases of his own and an analysis of the reported instances of cyanotic heart disease with continuous murmur E H Roche (Auckland N Z) concludes that this clinical picture most often indicates the presence of an atretic pulmonary artery compensated mainly by large arterial anastomoses In most reported cases these anastomoses were bronchopulmonary Quite rarely a continuous murmur in cyanotic heart disease indicates a primitive truncus arteriosus in which the developing pulmonary artery fails to join either the ventral or the dorsal aorta In such cases there will be no pulmonary branches in the truncus and no ductus arteriosus and the main blood supply to the lungs must be derived from the bronchial arteries In some of these cases it is to be expected that there will be bronchopulmonary anastomoses and continuous murmurs

In one patient the atretic pulmonary artery was compensated for by a knuckle of artery about ¼ in in diameter located just beneath the parietal pleura It was thought to come from the

(5) A t las Ann M d 2 17 21 M y 1953

whether or not dyspnea and cyanosis occur and are relieved by squatting In the infant rapid relief of dyspnea and improvement in color and irritability when he is placed in the knee chest position or held with the knees firmly pressed into the abdomen are diagnostic signs Certain other anomalies—certain instances of truncus and pseudotruncus arteriosus tricuspid atresia and single ventricle with rudimentary outflow chamber into the pulmonary artery—are relieved by squatting They share conditions similar to those in tetralogy namely high systemic flow low pulmonary flow and absence of cardiac failure They can be differentiated from the tetralogy by the cardiac contour

During the wait for definitive surgery demonstration and encouragement of postural relief is important therapy

Six Cases of Single Ventricle with Pulmonary Stenosis are reported by Maurice Campbell Geoffrey Reynolds and J R Trounce[4] who also report 1 case of bilocular heart with pulmonary atresia and review 78 reported cases of single ventricle This anomaly is to be distinguished from tricuspid or mitral atresia and a diminutive right or left ventricle although in such situations the larger ventricle is essentially the only functioning one Clinically patients with single ventricle have no regularly distinguishing features from the tetralogy of Fallot Actually they fulfil the criteria for there are pulmonary stenosis and a ventricular septal defect so large that there is but one ventricle the aorta is *functionally overriding in* that it takes blood from both sides of the heart and electrocardiographic and radiologic evidence suggests right ventricular hypertrophy

Each patient in this study had a systolic murmur in the pulmonary area in no case was a diastolic murmur heard The pulmonary second sound was of no aid in diagnosis Cardiac enlargement was not always present On fluoroscopy the left ventricle as well as the right often seemed enlarged The aortic arch was left sided in all cases Except for one case with a QRS interval of 0 11 second there was no bundle branch block in the ECG of any patient The bundle of His or equivalent conducting tissue must therefore be present somewhere despite the absence of an intraventricular septum

In the *reported cases of single ventricle* 46 were in males and 30 in females sex of the remaining 9 was not mentioned More than half the patients died before age 1 but 18 reached

(4) Guy s Hosp Rep 10 99 139 1953

a large central or eccentrically located and multiple septal de fect persistent foramen ovale and interatrial communication associated with anomalous entry of pulmonary veins into the right atrium or superior vena cava The authors consider these congenital defects technically suited for repair by modifications of the basic atrioseptopexy The Lutembacher syndrome—mitral stenosis with interatrial communication —can be cor rected by commissurotomy through the right auricle and the interatrial defect followed by atrioseptopexy in a one stage operation

TECHNIC —With the patient supine tran verse incision is made over the right anterior thorax for wide exposure of the fourth inter space The right lung is compressed and the pericardium opened widely A purse string suture is placed with nontraumatic needle in the greatly dilated right atrial appendage the ungloved left index finger is in erted through an incision within the purse string en closure for digital exploration of the accessible interior of the heart Then mitral commissurotomy if needed is performed To begin atrioseptopexy proper the finger is withdrawn to the terminal phalanx and overlapping sutures are placed from the lateral atrial wall into the lumen of the right atrium through the septal remnant then back through the septal remnant and through the atrial wall thus producing a mattress suture effect The atrial wall is thereby invaginated and approximated by circumferential sutures to the septal remnant to bridge the defect and yet leave a doughnut shaped right atrium with a lumen adequate for cardiodynamics

In hearts with anomalous pulmonary drainage into the superior vena cava or the right atrium the atrial wall i approximated only to the anterior lip of the septal remnant th line of sutures con tinuing to approximate anterior and posterior atrial walls so as to isolate pulmonary venous drainage from caval flow The pulmonary venous return then passes through an isolated portion of the right atrium through the still patent interatrial d fect and into the l ft auricle The procedure i suitably modified for correction of variants of interatrial eptal defects

Operative mortality among 19 patients with a defective septum secundum so corrected was 10 5% The survivors ex perienced notable clinical improvement Of nine patients with persistent ostium primum four died at least three of them as the result of such unrelated factors as myocardial hypothermic depression renal shutdown and very poor general condition The authors do not feel that the operation itself need entail a great mortality rate

descending aorta and anastomose with the left pulmonary artery In the second patient there was an atretic pulmonary artery and posteriorly there was a greatly enlarged bronchial artery coming off the right sided aorta and passing behind the esophagus entering the hilus of the left lung There was no ductus arteriosus It was decided to anastomose the left subclavian artery to the left pulmonary artery and both of these vessels were clamped The patient died and at autopsy the large *bronchial artery was found anastomosing directly with a primary* branch of the left pulmonary artery within the hilus of the lung thus supplying blood not only to the left lung but via the left and right pulmonary arteries to the right lung as well Therefore when the clamp was put on the left pulmonary artery at operation it occluded the circulation to the right lung as well The left lung having been deflated to expose the operative field there was irreparable embarrassment to rspiration by the occlusion of the left pulmonary artery In the third case a *distended vessel was found in the lingular region* which obviously received blood directly from the bronchial system The proximal atretic end of the pulmonary artery was clamped and as no deterioration in the pulmonary circulation ensued a subclavian anastomosis was performed with good results

The danger of occluding the pulmonary artery on the same side as the main arterial supply is illustrated by the second case When a Blalock Taussig operation is undertaken in such a case the author recommends that the chest be opened on the side on which the murmur is less easily heard A trial clamping of the pulmonary artery should be made to ascertain whether or not the remaining portion of the pulmonary circulation is sufficient to maintain life

Atrioseptopexy for Interatrial Septal Defects is relatively simple plastic surgery that can close nearly all types of atrial septal communication by bridging the defect with a portion of invaginated right auricular wall Charles P Bailey Houck E Bolton William L Jamison and Wilford B Neptune[6] (Hahnemann Med College) review the pathologic anatomy of such communications including the so called single atrium the persistent ostium primum central defect of the atrial septum (defective development of the septum secundum)

(6) J Th   n S   g 26 184 219 A   gu t 1953

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Effect of Short Term Administration of Corticotropin in Active Rheumatic Carditis Residual damage in rheumatic carditis usually depends on the duration and severity of the inflammatory process Because duration is variable evaluation *of the effect of corticotropin is simplified by restricting treatment to a period of time* significantly less than its usual course May G Wilson Helen N Helper Rose Lubschez Katharine Hain and Nathan Epstein[7] (New York Hosp Cornell Med Center) report the results of this regimen in 28 patients aged 3½ 18 with 32 attacks of active carditis who received corticotropin intramuscularly 1 5 mg /kg /day for 4 12 days If the circulating eosinophil count remained between 0 and 10/cu mm during the period of therapy dosage was arbitrarily considered adequate Results were compared with observations *made on seven patients who did not receive the drug*

Adequate corticotropin therapy was given 24 patients with active carditis None showed evidence of increased cardiac damage during therapy 22 had actual reversal of chamber enlargement The two patients who did not show reversal of chamber enlargement had had no progressive enlargement during the control period All patients were ambulatory within three weeks after therapy was discontinued Cardiac status was maintained 3 26 months in most cases for more than 6 months Two patients had minimal recurrences of active carditis when therapy was discontinued but there was spontaneous regression in about a week Four had recurrence of other manifestations (i e fever arthralgia) for several days but no evidence of associated active carditis

Of eight patients who had inadequate therapy by the standards adopted seven showed reversal of cardiac enlargement Five had recurrences of active carditis three of these received second courses of corticotropin in adequate dosage and in two the carditis spontaneously regressed One patient with carditis of more than 10 days duration did not show progressive enlargement during the control period and did not exhibit reversal of cardiac enlargement The sedimentation rate remained ele

(7) A M A Am J D Child 86 131 146 Aug t 1953

vated for weeks in most patients when they were ambulatory and had no evidence of diminished cardiac reserve or progressive cardiac damage and this elevation was not by itself considered evidence of active carditis

The controls showed no reversal of cardiac enlargement and signs of active carditis persisted from 10 days to 4 months Three had progressive cardiac enlargement

[These results are more favorable than many of those reported in the literature Most of the reports point toward favorable results from corticotropin in adults but less favorable results in children Perhaps the lack of improvement experienced in children may be related to inadequate dosage and to failure to push the hormone until well marked eosinopenia has been demonstrated —Ed]

Reactivation of Rheumatic Fever Following Mitral Commissurotomy may be more widespread than is generally recognized Louis A Soloff Jacob Zatuchni O Henry Janton Thomas J E O Neill and Robert P Glover[8] (Temple Univ) report this phenomenon in at least 24% of 179 patients considered free from active rheumatic heart disease at the time of commissurotomy Pain and fever are the cardinal symptoms in this syndrome The pain is generally precordial with occasional radiation to back epigastrium shoulder neck or jaw and has been described as dull aching bone crushing excruciating knife or viselike or as a severe tightness It is usually aggravated by postural change deep breathing and swallowing The pain may last 10 days to 4 weeks and may recur periodically The fever which usually rises slowly to 100 or 102 F persists 10 days to 4 weeks Adrenocorticotropic hormone tends to be antipyretic in such cases

With pain and fever there may be progressive heart failure arrhythmia arthritis hemoptysis or psychosis When heart failure appeared objective signs of right ventricular failure predominated and cardiac tamponade was considered a contributory factor in some cases In three patients the failure was intractable and fatal Autopsy in one case disclosed active rheumatic carditis The arthritis tends to be migratory and unaccompanied by objective manifestations of inflammation The arrhythmias noted were ventricular tachycardia multiple ventricular ectopic beats paroxysmal auricular tachycardia auricular fibrillation and auricular flutter Four patients had unexplained psychoses and two had hemoptysis

(8) C cul t 8 481 493 Oct be 1953

The ECG changes noted during the febrile postcommissurotomy syndrome were (1) occasional prolongation of A V conduction time (2) S T segment changes suggestive of pericarditis (3) S T changes suggestive of increased myocardial derangement (4) lowering of T voltage and prolongation of Q T also suggestive of increased myocardial derangement (5) transitory or permanent auricular fibrillation (6) increased ventricular rate and (7) auricular or ventricular ectopic beats or both Other studies disclosed inconstant leukocytosis and moderate increase in sedimentation rate Blood throat sputum and urine cultures were sterile

The pathogenesis of this syndrome is unknown It is common after mitral commissurotomy but not after nonrheumatic cardiac or pulmonary surgery and can be considered a reactivation of rheumatic fever

Left Atrial and Pulmonary Capillary Venous Pressures in Mitral Stenosis were measured consecutively by R G Epps and Richard H Adler[9] who found that regardless of the pressure level the mean pressures in the blocked pulmonary artery (pulmonary capillary venous pressure P C V P) were the same as the mean left atrial pressures Seven patients with mitral valve disease including sinus rhythm auricular fibrillation high and low left atrial pressures and high and low pulmonary arteriolar resistance were examined Mitral stenosis was present in five patients mitral stenosis and insufficiency in one and only mitral insufficiency in one

METHOD —An apparatus with a three way stopcock alternately permitted immediate registration of pressure in either arm of a Y shaped device One arm of the Y was connected to a polyethylene catheter introduced through a bronchoscope suction tube with a 22 gauge needle attached the other arm was a cardiac catheter Cardiac catheterization was performed while the patient was conscious and pulmonary artery pressure and P C V P were recorded under resting conditions The catheter was withdrawn to a main branch of the pulmonary artery and the bronchoscope introduced The needle on the tip of the polyethylene catheter was inserted in the left atrium through a point 1 5 mm distal to the carina on the medial wall of the left main bronchus The precise point was predetermined by radiologic study of the left atrium carina and left main bronchus and confirmed by direct inspection The needle was inserted midway between anterior and posterior walls of the left main bronchus thus avoiding the pulmonary artery anteriorly and

(9) B t H a t J 15 298 304 J ly 1953

esophagus posteriorly The cardiac catheter was advanced until it again blocked a peripheral pulmonary artery and the P C V P tracing was obtained Left atrial pressure was recorded immediately by turning the stopcock The procedures were repeated while the patient held his breath

All the P C V P tracings showed venous pulse waves similar to those from the left atrium Left atrial pressure pulses showed small c waves regardless of rhythm but these were less evident in P C V P records All pressure waves obtained from a blocked peripheral pulmonary artery showed a delay of 0 02 0 08 seconds when timed in relation to corresponding waves from the left atrium

Since pressures are labile recording of P C V P and left atrial pressures in immediate succession is necessary The mean P C V P and left atrial pressure were the same at all pressure levels No complications from left atrial puncture ensued al though two patients experienced a considerable rise in P C V P after bronchoscopy This emphasizes the potential danger of the procedure The authors believe that they have confirmed the view that the P C V P measured by cardiac catheterization is an accurate measurement of the left atrial pressure in mitral valve disease

Differential Diagnosis of Mitral Stenosis Clinicopatho logic Review of Simulating Conditions According to Jesse E Edwards[1] (Mayo Clinic) the incompletely emptied failing left ventricle is a barrier to pulmonary venous return but may be differentiated from mitral stenosis by signs of left ventricular enlargement Dilatation of the left ventricle produces tension on the chordae and interferes with closure of the mitral valve Constrictive pericarditis produces functional consequences in the lesser circulation and right ventricle identical with those of mitral stenosis Primary endocardial sclerosis a congenital fibrous thickening of the left ventricular endocardium constricts that chamber and impedes its filling

Pedunculated tumors of the left atrium may intermittently obstruct the mitral orifices and produce presystolic murmur Lesions of diverse cause which allow regurgitation through the mitral valve are prominent Healed bacterial endocarditis may permit back flow through the damaged valve leaflet and a congenital cleft in the mitral valve can produce similar in

(1) Lab I t 3 89 115 M Ap 1954

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(9) B t Hea t J 15 298 304 J ly 1953

due to left atrial failure it is precipitated by any factor which temporarily increases the cardiac output with the right ventricle pumping more blood into the lungs than the left ventricle can accommodate This mechanism is to be distinguished from the paroxysmal dyspnea of left ventricular failure which largely depends on a hypervolemic state with localization of congestion in the lungs because of left ventricular inadequacy These paroxysmal attacks are alarming and dangerous When dyspnea from noncardiac causes is difficult to differentiate from the dyspnea of mitral stenosis the demonstration of pulmonary hypertension which increases on exertion strongly supports mitral stenosis Pulmonary hypertension does not develop in bronchiectasis chronic bronchitis or emphysema unless lesions are severe Pulmonary edema is uncommon in later states of mitral stenosis probably because increased pulmonary arteriolar resistance has a protective effect or right ventricular failure has diminished the force of the pump

Patients with mitral stenosis are unusually susceptible to acute bronchitis However if apparent bronchitis is accompanied by undue dyspnea and nonpurulent sputum the diagnosis is questionable and pulmonary congestion and edema are likely to be present Hemoptysis is most common in patients with pulmonary hypertension and is particularly likely to occur during pregnancy Pulmonary infarction another cause of hemoptysis may follow emboli from the leg veins or the right heart or may be a consequence of pulmonary congestion alone Of the 100 patients 47 had a history of hemoptysis independent of pulmonary edema Hemoptysis is a strong indication for considering valvotomy

Fainting occurred in 12 patients In some the syncope was apparently exertional and due to the well established paradoxical action of the heart with mitral stenosis of decreasing cardiac output with exertion Paroxysmal auricular fibrillation itself or the asystole of transition between normal rate and tachycardia is another cause of syncope Some fainting of course may be caused by anxiety

Three kinds of pain are common in these patients (1) There is the noncardiac periapical (left mammary) pain also found in patients with cardiac neurosis This is generally aching stabbing of long duration and unaffected by nitroglycerin (2) There is a paradyspneic pain a sensation of retrosternal op

competence Ruptured or anomalous chordae can cause faulty alinement of the valve leaflets

In the congenital triatrial heart in which the pulmonary veins drain into an accessory cardiac chamber situated above the left atrium the isthmus between the chambers constitutes a barrier to pulmonary venous return Healed constricting mediastinitis produces a comparable hemodynamic abnormality

Combined lesions must be considered in the diagnosis of mitral stenosis In Lutembacher s syndrome—mitral stenosis and interatrial septal defect—mitral presystolic murmur may occur even when pulmonary capillary pressure is normal Mitral insufficiency may be associated with interatrial septal defect or with the so called corrected transposition of the great vessels

[Aside from the conditions mentioned, there is another which may at times be difficult to differentiate from mitral stenosis This is primary pulmonary hypertension associated with a presystolic gallop which may mimic closely the presystolic rumble of mitral stenosis Striking left auricular enlargement is strong evidence of mitral stenosis However in some patients the fluoroscopic findings concerning this point may be quite inconclusive Both disorders are characterized by elevated pulmonary arterial pressure but the pulmonary wedge pressure is elevated in subjects with mitral stenosis and not in patients with primary pulmonary hypertension However there may be such pronounced secondary pulmonary insufficiency that the catheter cannot be kept in the pulmonary artery and continually regurgitates making measurement of pulmonary wedge pressure impossible When doubt remains after exhaustion of all diagnostic procedures exploration of the left auricle may be justifiable — Ed]

Mitral Stenosis Diagnosis and Treatment Andrew Logan and Richard Turner (Univ of Edinburgh) report on 100 patients aged 16 59 in whom valvotomy was performed for predominant or pure mitral stenosis Historic and clinical aspects of the disease were evaluated in the light of actual findings at surgery and the benefits obtained from operation

Progressive exertional dyspnea is an indication for considering operation There is danger of attaching too little importance to a complaint of dyspnea since tight mitral stenosis and pulmonary hypertension may be present although the heart is of normal size and there is no manifest congestion of the lungs at time of examination Orthopnea indicates severe pulmonary congestion and therefore either tight mitral stenosis or severe myocardial damage Paroxysmal dyspnea of mitral stenosis is

( ) Lancet 1 1007 1018 May 23 1953 1057 1064 May 30 1953

pure mitral stenosis have small peripheral pulses and the hands are usually cold

Auricular fibrillation develops sooner or later in most patients with mitral stenosis most commonly precipitated by rheumatic carditis acute infections and perhaps exertion If active carditis is not present the onset of auricular fibrillation is an indication for considering operation since it represents progression of the disease Operation is probably better done before attempt is made to restore normal rhythm so that any loose clot is removed from the auricle and atrium

Radiography for evaluation of chamber size is indispensable The presence of calcification in the mitral valve is important but the systolic expansion of the left atrium has been of little benefit to the authors being nonspecific except in the presence of gross systolic expansion which certainly suggests mitral insufficiency In such cases however the diagnosis can be made on other grounds

Evidence on ECG of left ventricular hypertrophy is definitely indicative of mitral insufficiency or systemic hypertension Contrariwise ECG findings of pure right ventricular hypertrophy have meant that predominant mitral insufficiency was not present despite other suggestive signs such as a loud systolic murmur Most of the patients had cardiac catheterization as well In patients for whom valvotomy was dubiously advisable presence of a high resting pulmonary artery pressure or one that went up promptly on mild exertion prompted the authors to recommend valvotomy Operation has not been recommended in patients with normal pulmonary arterial pressure which did not rise on exertion

Patients aged 20 50 were considered the most suitable for operation No asymptomatic patient was operated on Mild aortic incompetence was not considered a contraindication and a third of the patients had signs of aortic incompetence Patients with obvious signs of rheumatic activity were not operated on but operation was performed on patients with borderline findings There is no evidence that operation necessarily aggravates the rheumatic process and delay in patients with tight stenosis may carry the greater risk

Preoperatively patients were instructed in breathing exercises Cardiac failure was corrected if possible Digitalis was given to patients with auricular fibrillation and quinidine was

pression or tightness often accompanying dyspnea It is not truly an exertional pain not being experienced apart from dyspnea (3) A pain said to be indistinguishable from angina pectoris may be felt on rest or exertion although there is usually no supporting ECG evidence of coronary arterial disease The authors consider this due to limitation of coronary blood flow consequent to mitral stenosis and pulmonary arteriolar resistance and to myocardial hypertrophy This type of pain occurred in two patients Pulmonary artery pressures were not specified for these patients

The typical sudden loud slapping first heart sound at the apex is so characteristic that its absence suggests predominant mitral insufficiency or else a tight stenosis with a rigid valve Accentuation of the second pulmonic sound is usually associated with severe pulmonary hypertension but hypertension in the lesser circuit occurs sometimes with a normal second sound as demonstrated by cardiac catheterization The loudness of this sound varies with exercise emotion and so on Apparent splitting of the second pulmonic sound is more often due to transmission of the opening snap of the mitral valve which is an important physical sign heard in most cases of mitral stenosis whether there is normal rhythm or auricular fibrillation

The characteristic mid diastolic murmur of mitral stenosis may appear to begin with the opening snap The authors did not find the presystolic murmur important The Graham Steell murmur is found only when there is severe pulmonary hyper tension and is therefore associated with an accentuated second sound and signs of right ventricular hypertrophy It is usually not so loud nor so long as the early diastolic murmur of aortic insufficiency is not conducted to the apex and may be in constant In general the systolic murmur of mitral insufficiency is long loud and harsh a fine high pitched apical systolic murmur unaccompanied by other signs of mitral incompetence can be ignored There are causes of loud apical systolic murmurs other than mitral insufficiency and even a loud mitral systolic murmur does not necessarily mean significant mitral regurgita tion

Right ventricular hypertrophy is best determined on physical examination by a thrust high in the epigastrium under the left costal margin or by a parasternal heave Patients with severe

loudest the second sound was not heard In some patients the murmur had a crescendo quality and was confined to late systole A soft short early diastolic murmur was heard medial to the apex or near the pulmonary area in 13 patients and had been present in 5 who later died no lesion of the semilunar valves was found at autopsy The second sound in the pulmonary area was frequently split the opening snap of the mitral valve was not heard The third heart sound was noted in 15 instances

Obvious systolic expansion of the left auricle seen in anterior and oblique views is the most important radiologic evidence of mitral incompetence Backward movement of the left auricle on the other hand is not a sign of incompetence because it is present in many cases of pure mitral stenosis

Left auricular enlargement was present in 26 cases Multiple ventricular extrasystoles were recorded by ECG in 12 patients in contrast with the frequency of auricular premature contractions in mitral stenosis The P waves were always normal Left axis deviation was present in 10 patients right axis deviation was never seen Half the patients had QRS T changes indicating left ventricular hypertrophy none had evidence of hypertrophy of the right ventricle

Autopsy on nine patients confirmed the clinical diagnosis of pure mitral incompetence Aschoff nodules were found in only one patient the remaining eight had varying degrees of scar tissue All had thickening and deformity of the valve cusps with some calcification in two

The characteristic features of pure mitral incompetence often permit a clinical diagnosis Because of frequent occurrence of bacterial endocarditis in these patients prophylactic penicillin therapy is required during surgery Heart failure though late in developing tends to progress rapidly

Commissurotomy for Rheumatic Aortic Stenosis I Surgery Rheumatic involvement of the aortic valve is second in frequency only to mitral valve involvement The pathologic developments in both tend to produce stenosis Commissural fusion begins peripherally (toward the annulus) and progresses centripetally sometimes eccentrically leading to stenosis with or without subsequent calcific deposition C P Bailey H E Bolton W L Jamison and H T Nichols[4] (Hahnemann

(4) C ul t 9 31 J rv 1954

given prophylactically to all patients with sinus rhythm The operation in every case was a division of the commissures digitally although in several instances use of a knife would have been advantageous In 26 of the patients with predominant mitral stenosis mitral regurgitation was found at cardiotomy as well At operation a clot was found in 20 instances The auricles were allowed to flush loose clots before valvotomy

Seven patients died as a direct result of the operation one as a result of incompatible blood transfusion All such losses were in patients with severe heart disease whose prognosis without operation was poor Another patient died of cerebral embolism after returning home Although follow ups are brief and a third of the patients had been followed less than six months most patients appeared to be much improved

Mitral Incompetence due to endocarditis as a solitary cardiovascular abnormality is characterized by Wallace Brigden and Aubrey Leatham[3] (London Hosp) from a review of the literature and study of 30 patients Only patients with a loud systolic murmur were considered and they were included if there was no ischemic heart disease hypertension anemia or other valve lesion Patients with a history suggesting rheumatic fever within five years and those under 20 were excluded confining the observations to patients with relatively static disease

Over half the patients were aged 50 60 Of the 5 women 3 had a history of rheumatic fever of the 25 men only 4 had such a history A third of the patients had had bacterial endocarditis superimposed on the valvular disease in sharp contrast with its relative rarity in pure mitral stenosis Nine patients had heart failure eight died

The only symptom of uncomplicated mitral incompetence was palpitation which was due to premature ventricular contractions The pulse was usually normal Auricular fibrillation was present in 5 patients 18 had clinical evidence of left ventricular hypertrophy none had the palpable accentuated first sound of mitral stenosis or any sign of right ventricular hypertrophy An apical systolic thrill was present in 19 On auscultation the first sound was normal The systolic murmur started at the first sound was transmitted to axilla and left scapular area but was always faint or absent to the right of the sternum Exactly at the apex where the murmur was

(3) B t H rt J 15 55 73 J u y 1953

degeneration is not an inevitable consequence of aging However the death rate from degenerative heart disease in the United States is not decreasing unlike the general trend in other diseases The generally poor mortality record of adults in the United States is fundamentally due to failure to control this disease according to Ancel Keys[5] (Univ of Minnesota)

The attempt to extrapolate to man the findings from cholesterol experiments with rabbits and chickens can lead to absurdities These animals have metabolic mechanisms for the handling of cholesterol that differ from those in man The typical experiment involving the rabbit an animal not naturally adapted to a high cholesterol diet specifies a diet which when extrapolated to man contains 10 15 times the amount of cholesterol in the ordinary high cholesterol diet

It is generally true that variations within the usual extremes of cholesterol concentration in the diet have little if any effect on the serum concentration of total cholesterol provided there is no essential change in calories total proteins or total fat in the diet On the other hand change in the total fat content of the diet—with other factors including cholesterol being constant—produces considerable change in the serum cholesterol concentration A comparison was made between a group of men in England and a group in Minnesota whose diets were similar in total fat but quite different in cholesterol intake Although the cholesterol portion of the diet of the group in England was not much more than half that of the Minnesota men the serum cholesterol concentrations were very similar This further validates the hypothesis that serum cholesterol is more closely related to fat intake than to dietary cholesterol There is no apparent difference between animal and vegetable fat in evoking the serum response

Other data also document the relationship between dietary fat and serum cholesterol (and lipoprotein) concentration and between these factors and the development of degenerative heart di ease Although the measurements of serum cholesterol and the S 12 20 concentrations in the serum in the various studies on this subject have little practical value for individual diagnosis or prognosis they have considerable significance in the differentiation of groups of men who are clinically healthy

(5) J Mt Sna H p 0 118 139 J ly A g 1953

Med College) believe that most cases of aortic stenosis are rheumatic in origin Congenital aortic stenosis is characterized by a funicular structure with absence of commissures A congenital bicuspid aortic valve may become the site of rheumatic stenosis In arteriosclerotic aortic stenosis with hardening of the valve leaflets and deposition of calcium salts there is no commissural fusion Endocarditis does not characteristically produce commissural fusion although it is often superimposed on a valve previously damaged by rheumatic disease

To treat aortic stenosis by commissurotomy the authors use a triradiate dilating head with a swivel mechanism which thereby alines itself automatically against the fused commissures An olivary tipped guide wire is incorporated into the dilator largely obviating the risk of making a false passage through the back of the heart Although the transventricular route has been used and reported on, a transaortic approach is preferable for young patients Patients with combined aortic *stenosis and mitral insufficiency should generally be operated* on through this approach with correction of the aortic lesion at the first stage The mitral lesions can subsequently be sutured from below although postoperative contraction of the incompetent valve may render the procedure unnecessary When aortic and mitral stenosis coexist both should be operated on through the transventricular approach in one stage In pure aortic stenosis the left ventricle is large and thick and the coronary circulation relatively inadequate Transventricular operation would appear to be a dangerous stimulus to fibrillation and in this group defibrillation is difficult by massage and electric shock because the muscle is so thick that manual expulsion of blood is difficult

Commissurotomy for rheumatic aortic stenosis is sound logical and effective and with greater experience may rank with mitral commissurotomy in safety and efficacy

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CORONARY DISEASE

Atherosclerosis Problem in Newer Public Health Degenerative heart disease a term used to include the conditions clinically diagnosed as angina pectoris coronary heart disease myocardial infarction chronic myocarditis and myocardial

degeneration is not an inevitable consequence of aging How ever the death rate from degenerative heart disease in the United States is not decreasing unlike the general trend in other diseases The generally poor mortality record of adults in the United States is fundamentally due to failure to control this disease according to Ancel Keys[5] (Univ of Minnesota)

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(5) J Mt S II p 20 118 139 J ly A g 1953

and groups of those likely to have coronary artery disease

The mechanism of the action of the diet on blood cholesterol concentration is not known There is no complete explanation for familial hypercholesteremia Factors other than serum cholesterol concentration probably play roles in the development of arteriosclerotic heart disease The influence of sex has not been determined For the 40 years of records available the proportion of fat calories in the total American food consumption has steadily increased concurrent with increasing incidence of degenerative heart disease These facts indicate a major problem in preventive medicine

Atherosclerosis—Inevitable or Controllable? Arteriosclerosis in North Americans begins in childhood The rate of lipid deposition in the intima of the arteries is highest during the first year of life and rises to two lower peaks in early adolescence and again in early middle age William Dock[6] (State Univ of New York) attributes this process to the inability of most human beings to deal with the modern high fat high cholesterol diet High fat diet with low cholesterol and good protein contents does not appear to lead to atherosclerosis in either man or animals Racial sexual and anatomic predilections to atherosclerosis have not been completely explained In males the coronary intima is thicker at birth than in females and *in both sexes at birth the intima is very much thicker in* the epicardial part of coronary arteries than in comparable arteries elsewhere in the body There is no evidence that obesity is a factor in human atherosclerosis

The atherogenic fraction of plasma cholesterol is apparently bound to beta globulin and involves molecules with a specific gravity between 0 98 and 1 022 (S_f 12 20) The total plasma cholesterol content bears no necessary relationship to the atherogenic fraction Estrogens have been shown to increase the cholesterol phospholipid ratio an apparently crucial relationship Heparin has also been found to retard atherogenesis in experimental animals if it is given in doses well below the level that affects clotting time There is a decline in the S_f 12 20 cholesterol

Ingestion of sitosterol (vegetable sterol) or dihydrocholesterol (synthetic sterol) *blocks the absorption of dietary* or biliary cholesterol in the bowel If cholesterol ingestion is

(6) Ca d M A J 69 355 363 O t b r 1953

an important factor in atherogenesis this observation is significant and as a result dietary precautions may at some future time be dropped Meanwhile a low fat low cholesterol liberal protein diet is recommended to offset the tendency to precocious onset of arteriosclerosis

Studies on Serum Cholesterol and Other Characteristics of Clinically Healthy Men in Naples were made by Ancel Keys Flaminio Fidanza Vicenzo Scardi Gino Bergami Margaret Haney Keys and Ferruccio di Lorenzo[7] in an attempt to elucidate the effects of lifelong subsistence on diets varying greatly in fat The studies were of 83 Neapolitan firemen and auxiliary police whose diets averaged 3 000 calories daily with about 20% fat compared with the 40% fat in the average diet in the United States which is about 3 130 calories Protein intake was approximately equal (90 and 97% average in the U S and Naples)

There was a marked age trend from 20 years to the early thirties serum cholesterol concentration rising about 3 mg/100 ml yearly The absolute concentrations and age trend closely resemble the findings in a large number of clinically healthy men in Minnesota After age 30 the trend diminishes rapidly and there is no significant further rise in the Neapolitan subjects whereas in the United States an average rise of 2 3 mg/100 ml continues into the fifties As a result the normal average at age 45 55 in the United States is about 30 mg/100 ml higher than in Naples Only a very small relationship was found between serum cholesterol level and relative obesity independent of age

ECG comparisons showed statistically significant differences between the Italians and the Minnesotans in regard to age trends The age trend to left axis deviation and prolongation of the PR interval and diminution of QRS and T potentials pronounced among the Minnesotans was small or lacking among the Italians

There is a great deal of evidence that the incidence of coronary and myocardial disease among middle aged men in the United States is far greater than in Italians This is of interest in view of the cholesterol and ECG data which show a consistent difference between the populations in the age range most characterized by coronary atherosclerosis The

(7) A M A Arch I t Med 93 3 8 336 M b 1954

authors conclude that the fat content of the diet has great significance in the serum cholesterol concentration and is related to the incidence of atherosclerosis and coronary heart disease

Effect of Dihydrocholesterol (Cholestanol) Administration on Plasma Cholesterol and Atherosclerosis in the Rabbit C W Nichols Jr M D Siperstein and I L Chaikoff[8] (Univ of California) having already proved that the addition of dihydrocholesterol (DHC) to the cholesterol containing diet of the chicken prevents hypercholesteremia and atherosclerosis investigated the effect action of DHC in the rabbit

METHOD —After a control period of feeding with a commercial diet for six weeks the rabbits were divided into four groups with the following dietary modifications group I no cholesterol and no DHC group II 1% cholesterol no DHC group III 1% cholesterol 2% DHC group IV no cholesterol 2% DHC Each diet contained 5% Wesson oil After two weeks on the experimental diets the commercial diet was again resumed because DHC was not available Five weeks later the experimental diets were restored and maintained for another nine weeks during which plasma cholesterol levels were measured several times The amounts eaten were not limited but each group consumed approximately the same amount The rabbits were killed after the experiment and each atherosclerotic plaque in the aorta was carefully measured and the total area estimated The total lipid content of representative liver samples was weighed

During the control period plasma cholesterol level was about 31 mg /100 ml for all groups During the experiment the average level in group I was very close to that in the controls no atherosclerosis was observed and total lipid content of the liver averaged 3 0% Group II had typical hypercholesteremia (average 1,041 mg /100 ml plasma) the average area of atherosclerotic plaques was 271 sq mm and average value for liver lipids was 6 7% In group III average plasma cholesterol level was 120 mg /100 ml average area of atherosclerotic plaques 4 9 sq mm and average value for liver lipids 4 6% In group IV (eight rabbits) average plasma cholesterol level was 28 mg /100 ml atherosclerotic plaques developed in only two of the rabbits but were large enough to average 19 8 sq mm for the group total lipid content of the liver averaged 3 3%

The addition of DHC to a normal diet does not depress plasma cholesterol levels but tends to prevent hypercholes

(8) P oc Soc. E per B l & M d 83 756 7<8 A g Sept 1953

teremia when cholesterol is added to the diet and appears to block the increase of lipid content of the liver

Experimental Atherosclerosis in Cebus Monkeys was produced by diets high in cholesterol and low in sulfur amino acids over periods of 18 30 weeks George V Mann Stephen B Andrus Ann McNally and Frederick J Stare[9] (Harvard Med School) devised modifications of a basic diet in which fat was supplied in corn oil and the cholesterol was a crystalline product obtained by solvent extraction from beef central nervous system The protein was either casein or α protein a soy bean product low in dl methionine

Normal serum cholesterol concentration was established by 103 determinations on 69 animals The mean was 112 mg /100 ml with standard deviation 51 mg Animals fed diets with 5% cholesterol and deficiency of methionine developed hypercholesteremia (300 800 mg /100 ml) but only if choline intake was adequate Hypercholesteremia is considered to be related to a sulfur amino acid deficiency and not to a so called methyl group deficiency This was further confirmed by the observation that daily supplementation of the methionine deficient high fat diet with dl methionine could prevent or reverse the hypercholesteremia

Autopsies on 17 animals fed high cholesterol α protein diets with adequate choline revealed cholesterol containing aortic lesions in 11 ranging from minimal to marked and usually positively correlated with duration of hypercholesteremia Autopsies on three animals fed similar diets but with deficient choline intake showed minimal aortic lesions in two None of the seven control animals had aortic lesions

Only one animal had a cellular fat containing plaque in the coronary intima but focal fat globules were found deep in the walls of small intramural coronary arteries in nine others with similar findings in small arteries in the spleen liver kidney adrenal gastrointestinal tract and testes No control animals had these fatty changes

Inhibition of Experimental Cholesterol Arteriosclerosis by Ultraviolet Irradiation was demonstrated in the rabbit by Rudolf Altschul[1] (Univ of Saskatchewan) who reported previously that irradiated egg yolk is less atherogenic in rabbits than untreated yolk

(9) J E pe Med 98 195 218 S pt mbe 1953
(1) N w E gl d J Med 249 96 99 J ly 16 1953

METHOD—Eighteen rabbits received daily 300 mg pure cholesterol or cholesterol heated for 30 minutes at 300 C for 90 days (one for 71 days) Ultraviolet irradiation was given for 10-60 minutes three times weekly at distances of approximately 40 cm Autopsy material included brain pituitary eyes tongue thyroid lung aorta heart thymus skeletal muscle skin stomach intestines liver spleen pancreas and gonads Serum cholesterol levels were determined at the beginning of the experiment in 14 animals and terminally in all Several hundred rabbits fed cholesterol in previous experiments served as controls and the cholesterol damage of irradiated rabbits was compared with what would have been expected on the basis of previous experiments

At the end of the experiment serum cholesterol content in irradiated animals was 18-1 415 mg/100 ml although only two values were over 733 mg Rabbits with the same cholesterol intake without irradiation almost regularly attain values greater than 1 200 mg/100 ml In most instances there was a striking inhibition of cholesterol damage which tended to parallel the effectiveness of irradiation in preventing a rise in serum cholesterol level In three rabbits one of the suprarenal glands showed extensive necrosis

The author believes that intense ultraviolet irradiation inhibits hypercholesteremia and mitigates or prevents cholesterol arteriosclerosis Ultraviolet irradiation may change the physicochemical nature of blood cholesterol causing it to lose its pathogenicity just as steroid hormones lose their hormonal property after irradiation Lumicholesterol formed under the influence of ultraviolet irradiation may be more readily excreted than cholesterol Under the influence of strong ultraviolet irradiation living or dying cells may produce proliferation promoting factors or biostimulators and these may in some obscure way affect cholesterol metabolism

Reduction of Blood Cholesterol in Man *can* be achieved with use of a plant sterol mixture (sitosterol) which interacts with ingested cholesterol to form nonabsorbable compounds O J Pollak (Quincy Mass) fed 5-10 Gm/day (in divided doses) of a plant sterol mixture containing 75-80% sitosterols to 26 subjects for 8 days to 8 months and to some subjects intermittently for as long as 14 months All participants had unrestricted diets Blood studies were done approximately once a week In all but one subject total blood cholesterol values decreased with the sitosterol regimen Minimal blood

(2) C cul t n 7 702 06 M y 1953

cholesterol level was reached within two weeks and was most easily achieved if the initial cholesterol concentration had been high No age or sex differences in response were noted although there were wide individual variations Continuous intake was necessary to maintain the low level of blood cholesterol

The patterns of the lowering of blood cholesterol values after sitosterol intake and after rigid restriction of dietary cholesterol as in a rice fruit diet are similar Both experiments show an irreducible residue of endogenous blood cholesterol

Sitosterol orally does not interfere with health or with the metabolism of any foodstuff other than cholesterol Ingestion of sitosterol can prevent intestinal resorption of cholesterol and result in lowering of blood cholesterol to basal endogenous level

[This report and the several preceding ones indicate some of the uncertainty surrounding the practical and important question of diet in patients with coronary disease Although considerable differences of opinion exist the evidence is becoming stronger each year that diet is important and that benefit may be produced by dietary methods If further studies by other authors confirm the results obtained by Pollak with plant sterol mixtures an important practical advance will have been achieved Patients naturally resent the insipid flavor of diets which are excessively low in cholesterol and many will not follow such diets conscientiously Therefore it would be particularly advantageous to be able to give the patient a normal diet and block the absorption of cholesterol It should be emphasized that some of the workers in this field believe that it is the fat in the diet rather than the cholesterol which is important in producing atheroma —Ed]

Effect of Estrogens on Plasma Lipids in Coronary Artery Disease was evaluated by M F Oliver and G S Boyd[3] (Univ of Edinburgh) in a study of hypercholesteremic male outpatients with coronary artery disease Blood samples were not taken in the fasting state but were obtained at the same hour of the day on each occasion After a small pilot study suggested that the possible effective dose of ethinyl estradiol would not be less than 0 2 mg daily 10 men were given 0 1 mg ethinyl estradiol at 12 hour intervals for two or three weeks The dose was then increased to tolerance indicated by gynecomastia listlessness fatigue and nausea The drug was given for 79 days with seven determinations of plasma lipids being made then inert tablets identical in size and shape were given for 6 weeks and three lipid determinations made The

(3) Am H t J 47 348 359 M b 1954

mean plasma cholesterol value had fallen an average of 25% by the end of administration of the drug phospholipid levels remained practically constant After the six weeks of inert tablets total cholesterol values rose an average of 35% The plasma total cholesterol phospholipid ratio fell an average of 29% during treatment and rose 40% after placebo administration

All patients had unpleasant side effects and all experienced a sense of well being when given inert tablets There was no definite change in the incidence or severity of effort pain or breathlessness

Effects of Exercise and Smoking on Electrocardiograms and Ballistocardiograms of Normal Subjects and Patients with Coronary Artery Disease To increase the specificity of laboratory tests designed to establish the diagnosis of coronary artery disease Frank W Davis Jr Wm R Scarborough R E Mason M L Singewald and B M Baker[4] (Johns Hopkins Univ) investigated a number of stress eliciting procedures with the ballistocardiograph (BCG)

METHODS —The two step exercise test was used with 200 persons 114 of whom were normal controls (aged 25 68) and 86 patients (aged 29 71) in whom coronary disease was evidenced by past myocardial infarction or the presence of unequivocal angina pectoris Normal persons first underwent a double test if results were abnormal a single test was done Patients with coronary artery disease first were given a single test and if the results were normal a double test was performed The ECG was recorded immediately at 3 and at 5 minutes after completion of the test BCG s were done 4 6 and 10 minutes after the test was finished The cigaret test was also tried among 200 persons some of whom were also included in the exercise test group of this group 118 were normal controls (aged 25 74) and the rest (aged 29 68) had coronary artery disease In this test the subject smoked a standard brand cigaret at his usual rate The BCG ECG and blood pressure readings of each patient were recorded before and five minutes after this test Also 10 persons were given pure nicotine sublingually (0 1 mg nicotine base in a vehicle) each minute for five minutes to determine the importance of nicotine in the production of ballistic changes after smoking For these tests the criteria of Master were used to judge ECG abnormality indicative of coronary artery disease In the BCG evaluations the result was considered positive if a normal tracing became abnormal or if an abnormal tracing became distinctly more so If deterioration failed to appear the result was considered negative

(4) Am Heart J 46 529 542 October 1953

The ECG response to exercise was positive in 22 8% of the normal controls (45 5% of normal women and only 13 6% of normal men) with no definite age trend noted Of the group with coronary artery disease 50% reacted positively this figure is maximal since patients with negative response to a single test had double tests Of the normal group 7 9% had positive BCG results after exercise as against 31 4% of the patients with coronary disease Correlation of the results of these two tests showed that 38 6% of normal persons of all ages had ECG or BCG abnormality or both either at rest or after exercise of the group with coronary artery disease 83 7% had at least one abnormal record

In the cigaret test 68% of the normal controls had positive BCG tracings as against 58 6% distinctly positive among patients with coronary artery disease Response to nicotine sublingually was generally similar to that on the cigaret test The authors conclude that the cigaret test serves better to differentiate patients from controls than the two step BCG or ECG test

[Attention is called to the high incidence of positive reactions in the normal subjects and to the high incidence of negative reactions in the patients with coronary disease These findings are in keeping with the editor s experience and indicate that the ECG responses to exercise as currently interpreted have relatively little value in the diagnosis of coronary disease and in fact are frequently misleading When on the other hand the criteria advocated by Wood *et al* (Brit Heart J 13 363 1950) are used the ECG response to exercise may be most valuable —Ed]

Ballistocardiograms after Cigaret Smoking in Health and in Coronary Heart Disease have been recorded by C B Henderson (Univ of Pennsylvania) using the Starr high frequency table Other investigators using the Nickerson low frequency damped ballistocardiograph have reported that cardiac output remained unchanged whereas experiments with the Dock direct body type have demonstrated changes in ballistic form after smoking

Method —Subject were 50 healthy adults aged 20-40 30 healthy adult 40-60 40 patient with coronary heart disease 2 with idiopathic hypercholesteremia 1 with Buerger s diseas and 1 with diabete mellitus with hyperten ion Following a control record each subject smoked a cigaret for one minute then briefly desisted while a second record was taken He then continued to smoke for four more minute at the end of which time a third record was made Three more record were made at five minute intervals

(5) B t H t J 15 8 286 J ly 1953

None of the healthy young adults displayed an abnormal ballistic contour either before or after smoking Of the 30 normal subjects 4 showed abnormalities of form All four inhaled three experienced tingling of the extremities nausea and vertigo In 21 of the 40 patients with coronary artery disease the initial records were abnormal Five of these became more abnormal and 10 of the 19 patients with normal records had abnormalities of form following smoking The four patients with miscellaneous diseases who were by the nature of their primary ailment more likely to develop coronary heart disease showed deterioration of wave form

Three general types of abnormalities were discerned Some subjects had a combination of I and J wave abnormalities consisting of a decrease in depth of the I wave and a decrease in height and deformity of the J wave In another group there was an increase in height of the H wave and the J waves became deformed or smaller than the H waves in some of the expiratory complexes In one patient the H and I waves decreased and the K wave increased in all phases of respiration In most cases the form of the ballistocardiogram reverted to the presmoking state 5 minutes after cessation of smoking in a few the abnormalities persisted longer than 15 minutes Inhaling the smoke was believed to have a greater effect than not inhaling

The author believes the alteration of cardiac function after smoking is due to coronary vasoconstriction

Cardiac Work and Chair Treatment of Acute Coronary Thrombosis were quantitatively evaluated by Walter S Coe[6] (Univ of Louisville) in six subjects three with normal cardiovascular systems and three with decompensated arteriosclerotic heart disease

Method —Dye (T 1824) was injected into the pulmonary artery through a cardiac catheter and serial arterial samples were obtained from an indwelling radial artery cannula Intra arterial pressures were obtained from the radial artery by means of an electromanometer The subject was first prone then the studies were repeated after he had been helped into a padded armchair Cross sectional area of each subject s aorta was obtained from age body surface graphs The mean circulation time was that time required for half of the dye to pass from the point of injection to the point of sampling Pulmonary blood volume (including left side of heart and arterial system to point of sampling) was calculated by multi

(6) A n I t Med 40 42 48 J uary 1954

plying cardiac output per second by mean circulation time Peripheral resistance was derived from the formula

$$R = \frac{P_m \times 1332}{V_t}$$

where P_m is mean arterial pressure in mm Hg V_t is cardiac output in cc /second and 1332 is a constant Cardiac work was determined by

$$W = QR + \frac{MV}{2g}$$

where Q is volume of systolic discharge M mass of ejected blood V velocity and g gravity (980 cm /sec) The mass of ejected blood was obtained by multiplying the volume of systolic discharge by the specific gravity of blood Velocity was calculated by dividing cardiac output/second by the cross sectional area of the aorta and squaring the result

Four of the six subjects had diminution in calculated pulmonary blood volume amounting to 685 cc in one patient In each hematocrit reading was slightly increased stroke volume was smaller and peripheral resistance greater while in the arm chair Mean reduction in cardiac index in the armchair position amounted to 0 73 L /sq m body surface or 21% Mean calculated cardiac work was reduced 23%

Cortisone in Treatment of Shoulder Hand Syndrome Following Acute Myocardial Infarction. Henry I Russek Allen S Russek Alexander A Doerner and Burton L. Zohman[7] (U S Pub Health Service Hosp Staten Island N Y) report results of cortisone therapy in 17 patients all of whom had had physical therapy manipulative therapy or local and stellate ganglion blocks without benefit All but four received 200 mg cortisone orally or intramuscularly in divided doses for two days with progressive diminution to a maintenance dose of 50 mg daily through the third week All were placed on a low salt diet

Five experienced complete relief from signs and symptoms eight had marked and three moderate improvement and one no relief Dramatic relief from pain often occurred in 24 hours and the range of motion at affected joints increased Decrease or disappearance of edema and improvement in color temperature and sudomotor activity of the hand followed cortisone therapy Discontinuance of therapy was not followed by a recurrence and no thromboembolic phenomena were observed

(7) A M.A A h I t Med 91 487-492 Ap 1 1953

None of the healthy young adults displayed an abnormal ballistic contour either before or after smoking Of the 30 normal subjects 4 showed abnormalities of form All four inhaled three experienced tingling of the extremities nausea and vertigo In 21 of the 40 patients with coronary artery disease the initial records were abnormal Five of these became more abnormal and 10 of the 19 patients with normal records had abnormalities of form following smoking The four patients with miscellaneous diseases who were by the nature of their primary ailment more likely to develop coronary heart disease showed deterioration of wave form

Three general types of abnormalities were discerned Some subjects had a combination of I and J wave abnormalities consisting of a decrease in depth of the I wave and a decrease in height and deformity of the J wave In another group there was an increase in height of the H wave and the J waves became deformed or smaller than the H waves in some of the expiratory complexes In one patient the H and I waves decreased and the K wave increased in all phases of respiration In most cases the form of the ballistocardiogram reverted to the presmoking state 5 minutes after cessation of smoking in a few the abnormalities persisted longer than 15 minutes Inhaling the smoke was believed to have a greater effect than not inhaling

The author believes the alteration of cardiac function after smoking is due to coronary vasoconstriction

Cardiac Work and Chair Treatment of Acute Coronary Thrombosis were quantitatively evaluated by Walter S Coe[6] (Univ of Louisville) in six subjects three with normal cardiovascular systems and three with decompensated arteriosclerotic heart disease

METHOD —Dye (T 1824) was injected into the pulmonary artery through a cardiac catheter and serial arterial samples were obtained from an indwelling radial artery cannula Intra arterial pressures were obtained from the radial artery by means of an electromanometer The subject was first prone then the studies were repeated after he had been helped into a padded armchair Cross sectional area of each subject s aorta was obtained from age body surface graphs The mean circulation time was that time required for half of the dye to pass from the point of injection to the point of sampling Pulmonary blood volume (including left side of heart and arterial system to point of sampling) was calculated by multi

(6) Ann I t. Med 40 42 48 Ja u y 1954

consistent with previous observations indicating an autonomy of tone of the renal arterioles

In most cases the changes in glomerular filtration rate follow a pattern similar to the alterations in renal plasma flow but occasionally filtration remains below control values Oliguria with increased concentration of urine usually occurs All of these renal effects begin to diminish after 30 60 minutes despite continued significant hypotension

Studies to date suggest that sympathetic vasoconstrictor nerves blocked by hexamethonium exert the controlling influence on homeostatic adjustments to postural change as well as in maintaining the tone of the vessels of the distal part of the extremities However in resting supine subjects such nerves appear to have a much less important influence on arteriolar tone in the hepatic portal renal and muscle areas

Studies on Control of Hypertension by Hyphex II Toxic Reactions and Side Effects John D Morrow Henry A Schroeder and H Mitchell Perry Jr[9] (Washington Univ) report on the side effects of 1 hydrazinophthalazine and hexamethonium chloride and a combined form (hyphex) in over 250 patients Untoward reactions to hexamethonium were all manifestations of autonomic ganglion blockade and could be controlled Constipation was the most troublesome others included orthostatic hypotension blurring of vision dryness of the mouth hypotonicity of the bladder impotence and intolerance to cold

Hydrazinophthalazine is an antihistaminase in vitro and many of its side effects are explained by liberation of histamine—stuffy nose periorbital edema lacrimation slight but diffuse edema headache generalized aching and prostration However more serious reactions occurred In six instances a severe febrile reaction followed administration of the drug Several other patients noted transient arthralgia In 16 patients a syndrome indistinguishable from rheumatoid arthritis occurred and if the drug was not discontinued features of disseminated lupus erythematosus developed Skin rashes abnormal liver function fever hematuria anemia leukopenia adenopathy splenomegaly hyperglobulinemia and albuminuria appeared in varying numbers of these patients No L E cells were found All recovered readily

On hyphex therapy five deaths occurred apparently

(9) Circulat 8 829 839 D mb 195

Cortisone was tried after treatment of similar hand and shoulder disorders in hemiplegic patients produced favorable results Case selection was considered from two aspects severity of clinical symptoms in cases refractory to other therapy and possible risk of untoward effects from cortisone

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HYPERTENSION

Hemodynamic Effects of Hypotensive Drugs in Man III Hexamethonium Subjects for this study by Edward D Freis John C Rose Edward A Partenope Thomas F Higgins Robert T Kelley Harold W Schnaper and Robert L Johnson[8] were 25 hypertensive and 4 normotensive patients Hexamethonium was given intravenously at the rate of 1 2 mg/minute for the first 15 mg then at the rate of 5 mg/minute until a significant hypotensive effect was obtained or until 50 100 mg had been administered The observations indicated that in hypertensive patients without cardiac decompensation reduction of systemic arterial pressure is accompanied by a decrease in right heart pressures and cardiac output Total peripheral resistance does not change significantly These alterations are probably the result of a combination of venous pooling and failure of reflex vasoconstriction In patients with heart failure the fall in systemic arterial pressure appears to be accompanied by a reduction of right heart pressures an increase in cardiac output and a significant decrease in total peripheral resistance These alterations may be due to unloading of the congested right side of the heart as well as to inhibition of vasoconstrictor reflexes activated by the low output heart failure

In contrast to the decided increase in blood flow in the foot observed previously blood flow through the muscles increases only moderately Since arterial pressure falls after administration of hexamethonium a significant decrease in peripheral resistance is assumed to occur in this area Despite a moderate reduction of hepatic vascular resistance estimated hepatic portal blood flow usually decreases after the drug is administered Renal plasma flow decreases paralleling the initial fall in arterial pressure then rises to approximate control levels despite a continued hypotensive response This is

(8) J Cl n In st. 3 1285 1298 D c mb 1953

hot weather although these could be consequences of sodium loss

Side effects were similar to those of other ganglionic blocking agents Collapse and paralytic ileus did not occur and constipation was not as severe as with hexamethonium The dru seldom accumulated in the gastrointestinal tract and absorption was even Nevertheless oral therapy with M&B 2050 as a single hypotensive agent leaves much to be desired because dosage adjustment must usually be meticulous and the dose requisite tor hypotensive action generally induces side effects

Recent Developments in Treatment of Hypertension are reviewed by Edward D Freis (Georgetown Univ) The ideal treatment for hypertension will be chemotherapeutic It should cause no serious toxic reaction and a minimum of disagreeable side effects Duration of hypotension should be at least eight hours permitting a normal period of sleep It should be inexpensive effective orally and the method of dosage adjustment should be uncomplicated practical and standardized No single agent or combination thus far has met these criteria although they are being closely approached

Ganglionic blocking agents inhibit transmission of impulses through all autonomic ganglions and so may produce postural hypotension increase in blood flow to distal extremities constipation hypochlorhydria atony of the urinary bladder impotence reduction in salivary and sweat gland secretions and failure of visual accommodation They also induce tolerance Intestinal absorption is poor and inconstant making dosage regulation difficult When patients are put on salt restricted diets the postural hypotension produced by these agents is aggravated

Rauwolfia serpentina and its derivatives are relatively simple to administer and do not induce severe side reactions Blood pressure reduction however is variable Side effects include sleepiness nasal congestion and bradycardia

Veratrum alkaloids act primarily on vagus nerve endings in the myocardium and carotid sinus to produce reflex bradycardia and vasodilation Dosages slightly in excess of or equal to the hypotensive dose may stimulate the emetic center The alkaloid cryptenamine apparently has a wider dosage margin in this regard

(2) M Cl N th Am 38 363 374 Ma h 1954

caused by pulmonary complications pathologically resembling interstitial pneumonia uncontrolled hypotension was responsible for death in one case and in another sudden death occurred

The complications of combined therapy are impressive and use of these agents might be restricted were it not for the almost uniformly fatal nature of malignant hypertension (to which interstitial pneumonia has been confined) and the relatively benign nature of the arthritis

Clinical Appraisal of Pentapyrrolidinium (M&B 2050) in Hypertensive Patients is presented by Edward D Freis Edward A Partenope Lawrence S Lilienfield and John C Rose[1] (Georgetown Univ) Pentapyrrolidinium (pentamethylene 1 5 bis [1 methyl pyrrolidinium bitartrate]) was found to be approximately *five times more potent than* hexamethonium in four hypertensive patients to whom each drug was given intravenously Average duration of action was 42% longer than that of hexamethonium and maximal hypotensive actions proceeded more gradually

Ten hypertensive patients were given M&B 2050 subcutaneously twice daily for a week then orally every 8 hours with doses slowly increased until the average daily blood pressure approximated that achieved during parenteral therapy The mean effective parenteral dose was 15 mg /day and the mean daily oral dose 280 mg This ratio is approximately the same as that reported for hexamethonium M&B 2050 *given orally had a more predictable onset of action than* hexamethonium (about an hour after administration) and there was less day to day variation of response to a given dose Tolerance to the drug was not as noticeable as with hexamethonium and there was insignificant cross tolerance between the agents

M&B 2050 was given orally to 27 patients as the sole medication for two to six months Over half the patients had blood pressure reduction of 60 mm Hg systolic and 30 mm diastolic 85% had diastolic reductions of 20 mm Hg or more Postural hypotension was prominent and ingestion of a large meal or of alcohol potentiated the effects of the drug Salt depletion caused exaggeration *of the hypotensive response and a similar* effect was noted following vigorous exercise and during

(1) C culat n 9 540 546 Ap 1 1954

patients with pheochromocytoma and persistent hypertension as well as those with paroxysmal hypertension during or between attacks

Laboratory methods consisted in part of adsorption of the urinary catecholamines on precipitated aluminum hydroxide followed by elution desalting and concentration in vacuo These extracts were studied by bioassay paper chromatography photofluorometric evaluation and absolute quantitation of nor epinephrine and epinephrine by chemical methods Photofluorometric evaluation of urine extracts seemed to be the most reliable test for pheochromocytoma

A short procedure consisting of adsorption of catecholamines in hydrolyzed urine on an aluminum oxide column followed by photofluorometric evaluation of the eluate can be used as a rough screening test When positive results are obtained the longer and more specific method must be applied for confirmation

No false positive or false negative results were encountered with the short procedure In an addition group of 44 patients with suspected pheochromocytoma the short screening procedure gave one false positive result but the long screening procedure gave a negative result In eight patients of this second group false positive responses to regitine* were obtained and in three false positive responses to histamine Pheochromocytomas were detected in six patients

Effect of Hydrogenated Alkaloids of Ergot on Hypertensive Headaches The headaches of hypertension that may be the most prominent complaint may also be associated with (1) arteriolar constriction and vasodilatation of the capillary wall resulting from anoxia (2) cerebral damage with arteriolar necrosis (3) toxemia resulting from renal failure and (4) other causes The vasodilating and sympatholytic properties of certain dihydrogenated alkaloids of ergot suggest their use to remedy this complaint Travis Winsor[4] (Univ of Southern California) reports a study of 86 patients with headache of whom 66 had hypertension (benign in 46 arteriosclerotic in 20) and 20 nonhypertensive headaches including 10 with migraine 4 due to spinal anesthesia 3 to sinusitis 2 to trauma and 1 to poliomyelitis Drugs used were the hydrogenated alkaloids of ergot dihydroergocornine dihydroergocristine

(4) G t 8 636 642 D emb 1953

Hydrazinophthalazine is unique in that it increases cardiac output and renal and total splanchnic blood flows Side effects include headache tachycardia dyspnea and occasionally angina Total daily dose should be below 500 mg since arthritis or a syndrome resembling disseminated lupus may appear when dosages are elevated beyond this level

Patients with mild hypertension can be treated with rauwolfia alone or in combination with veratrum or hydrazinophthalazine For those who do not respond to this management a comb nation of 0 2 mg serpasil® 15 mg prostigmin 25 80 mg pentapyrrolidinium and 20 90 mg hydrazinophthalazine is administered

[The advances in the use of hypotensive drugs in the past few years have been dramatic These agents will accomplish everything that sympathectomy will and may be discontinued if untoward side effects occur Therefore there seems to be practically no place for sympathectomy in the treatment of hypertension at the present time On the other hand as is indicated in the preceding articles the hypotensive drugs are capable of eliciting serious toxic reactions They should be given with the greatest care and it is decidedly advantageous to start them when the patient is in the hospital for a period of two or three weeks in order that optimal dosage may be determined It is probable that pentapyrrolidinium will eventually replace hexamethonium although more information is needed on this point The rauwolfia compounds may be sufficient alone for the milder instances of hypertension and particularly when there is a large psychogenic component However patients with the more severe cases appear to do best when treated with a combination of rauwolfia apresoline® and either hexamethonium or pentapyrrolidinium —Ed]

Chemical Screening Methods for Diagnosis of Pheochromocytoma I Nor Epinephrine and Epinephrine in Human Urine Marcel Goldenberg Irving Serlin Theodora Edwards and Maurice M Rapport[3] (Columbia Univ) studied the urinary excretion of catecholamines (nor epinephrine and epinephrine) in 16 patients with pheochromocytoma 91 with essential hypertensive vascular disease 13 normotensive healthy subjects 10 with Addison s disease and 14 with essential hypertension following thoracolumbar sympathectomy The source of nor epinephrine in human urine is the sympathetic nervous system Only a small fraction may be derived from the adrenal medulla Patients with pheochromocytoma consistently excreted epinephrine and/or nor epinephrine in excess of amounts excreted by normotensive or essential hypertensive subjects Excess urinary excretion was found in

(3) Am J M d 16 310 3 7 M ch 1954

month Group II (45 patients) previously digitalized with and maintained on digitalis leaf digitoxin or digoxin was transferred to gitalin therapy Group III (eight patients) could not be given digitalis leaf digitoxin or digoxin in effective amounts because of toxicity Gitalin was substituted for the offending preparation and rapid improvement followed

No toxicity was encountered in any of the 68 patients during gitalin therapy Experimental work by other investigators shows that toxicity is generally similar to that caused by other digitalis preparations

[The claim that a given digitalis preparation has a more favorable toxic therapeutic ratio than other preparations has been often made and hence is naturally viewed with skepticism However a number of different investigators have now substantiated this claim so far as gitalin is concerned Available evidence suggests that this preparation is the most generally suitable one for oral use in the majority of patients —Ed.]

Experimental and Clinical Investigations on Cardiac and Circulatory Effects of a New Glucoside Free Digitalis (Acetyl digitoxin) H Ph Hausler and W Hoertnagl[6] (Vienna) studied 42 patients with circulatory insufficiency of various etiologies (valvular defects myocardial diseases decompensated hypertension) A 1 cc solution (30 drops) contained 0 5 mg of the glucoside free acetyldigitoxin

Oral administration of 20 drops (0 33 mg) of acetyldigitoxin to previously untreated fasting patients led to circulatory response in some cases within 5 minutes and unquestionably in 10 20 minutes In mitral valvular defects and aortic stenosis there was an average rise of 12% in systolic blood pressure and an average drop of 9% in diastolic By contrast in aortic insufficiency systolic pressure fell 8% and diastolic rose 6% There was a decrease in stroke and minute volume in aortic insufficiency and an increase of these factors in the other valvular defects In mild myocardial diseases systolic pressure rose 9% and diastolic fell 2% The rate decreased from 79 to 62 beats per minute and there was a corresponding drop in minute volume Myocardium damaged by toxicity or multiple infarcts showed a drop in the systolic pressure and a great decrease in stroke and minute volume with slight changes in heart rate Decompensated hypertensive patients reacted well subjectively and objectively

In all cases of valvular defects (except aortic insufficiency)

(6) Wien kl Wchschr 65 473 475 May 29 1953

and dihydroergokryptine (CCK 179) combined in equal amounts in a 0 5 mg sublingual tablet Placebos of the same size and color and 0 66 Gm tablets of aspirin were used Dosage of CCK 179 was 0 5 1 0 mg three times daily for many months

Of 42 patients with hypertensive headaches 86% were completely or partly relieved 19% of those given only placebos obtained partial relief half of those who took aspirin alone had complete or partial relief Half of those given aspirin and CCK 179 alone or in combination had more relief from the two agents together None of those with nonhypertensive headache due to miscellaneous causes obtained relief Of the 10 patients with migraine 8 had fewer attacks after CCK 179 therapy

Judged by the vasodilating effect on the finger tips the action of CCK 179 lasts a little longer than an hour although relief from hypertensive headaches is more prolonged

CONGESTIVE FAILURE AND SHOCK

Clinical Evaluation of Gitalin in Treatment of Congestive Heart Failure is presented by Sim P Dimitroff George C Griffith M C Thorner and Joseph Walker[5] (Univ of Southern California) Although this amorphous derivative of Digitalis purpurea has been isolated for 40 years only recently has its particular merit of having a low therapeutic ratio (therapeutic dose/toxic dose × 100) been recognized Toxicity from gitalin does not last as long as that caused by the whole leaf or by digitoxin

Two methods of rapid digitalization may be used 1 mg three four or six times daily until digitalization is achieved or 2 5 mg initially followed by 1 mg every four to six hours until the effects are obtained Average digitalizing dose is about the same in each—6 6 5 mg with therapeutic effect attained in 24-48 hours The slow method consists of 0 5 mg three or four times a day until improvement or toxicity appears four to seven days are usually required The authors report on 68 patients Group I (15 patients) was given only gitalin no other digitalis preparation had been taken during the preceding

(5) A n I t M d 39 1189 1199 D mb 1953

and in the normal subject several weeks are required for the body to rid itself of digitoxin Daily urinary excretion in patients taking 0 1 mg daily is 32-44 μg Less than 10% is excreted by the biliary system Extrarenal processes can maximally excrete or destroy only about 50 μg daily If the maintenance dose of digitoxin is higher renal excretion is increased but is itself limited Thus intoxication is rather readily obtained

Digitalis Intoxication an increasingly common phenomenon since the introduction of potent cardiac glycosides was discussed by staff members of the Veterans Administration Hospital Bronx at a clinical conference arranged by Arthur C DeGraff[8] Toxicity may result from overdosage too frequent administration failure to recognize that with maintenance therapy there is a slow accumulation of digitalis in the body and vigorous use of mercurial diuretics Digitoxin given intravenously does not achieve maximal effect for eight hours and should not be given at more frequent intervals It is apparently particularly prone to show cumulative action Failure to pay attention to the early signs or symptoms of overdosage—specifically personality change anorexia or nausea—is a common cause of intoxication

As heart disease progresses there is progressive narrowing of the margin of safety until the toxic dose is less than the therapeutic one

If digitalis intoxication is suspected in a patient the best procedure is to withhold the drug and observe the patient Overdosage with digitalis can produce congestive heart failure which will spontaneously clear when the drug is withheld Ventricular tachycardia and extrasystoles produced by digitalis can be treated with procaine amide quinidine or potassium procaine amide possibly being preferable

A patient with acute myocardial infarction and congestive heart failure should be digitalized very slowly unless rapid digitalization is particularly indicated When premature ventricular contractions occur in a digitalized patient with myocardial infarction it may be difficult to determine whether they are due to the necrotic tissue or to digitalis

In most patients it is not necessary to digitalize to toxicity and then reduce the dosage this may be advisable however

(8) Circulation 9 115 126 January 1954

myocardial diseases and decompensated hypertension ratio of ejection time contraction time increased denoting improvement in cardiac function Circulation time venous pressure and vital capacity improved About an hour after the initial administration of acetyldigitoxin there was an increase of the conduction time After administration of 15 drops three times a day for six to eight days there was definite downward displacement of the S T segment The S T segment became isoelectric after therapy was discontinued for three days Signs of failure reappeared depending on initial and maintenance dosage used within 6-12 days after cessation of therapy Except for changes in the S T segment there were no signs of toxicity extrasystoles or bigeminy *It was possible to decrease paroxysmal* tachycardia with oral administration of 20 40 drops of the drug The glucoside seems to have a diastolic cardiac effect

Behavior and Fate of Digitoxin in Experimental Animal and Man are discussed by Meyer Friedman Shirley St George and Rene Bine Jr[7] (Mount Zion Hosp San Francisco) Digitoxin is a typical cardiac glycoside which can be hydrolyzed to digitoxigenin and three molecules of digitoxose A similar *equilibrium distribution obtains whether the drug* is ingested or injected implying complete absorption with little or no destruction in the process of absorption Cardiac failure does not appear to impair absorption Digitoxin is partially adsorbed by serum albumin and tends to disappear rather slowly from the blood as compared with lanatoside C This suggests that lanatoside C by its property of becoming more rapidly available from its protein bound state is preferable for rapid digitalization Cardiac tissue apparently has no greater affinity for digitoxin than has liver lung or kidney tissue Little or no digitoxin is present in extracellular fluid Thus the toxic effects following rapid reabsorption of extracellular fluid arise from other causes

Evidence indicates that the failing heart exhibits a discrepancy between the amount of chemical energy potentially available and that which is mechanically utilized In some unknown manner digitoxin improves the diminished response of the total contractile mass to the undiminished supply of chemical energy and may possibly have an effect on the actin myosin actomyosin reaction Renal excretion is slow

(7) M d ci 33 15 41 F brua y 1954

Electrolyte Disturbances in Congestive Heart Failure Clinical Significance and Management are discussed by William B Schwartz and Arnold S Relman[1] (Boston) In most patients given mercurials the eliminated fluid contains more chloride than sodium the difference between the two usually being made up by potassium and/or ammonium A generally asymptomatic hypochloremic alkalosis is produced the chief importance of which is that it may result in refractoriness to further mercurial therapy Even changes in chloride and bicarbonate concentration as small as 4 6 mEq /L may affect the diuretic response Intravenous infusion of a 1% solution of ammonium chloride in a 5% glucose solution at a rate not in excess of 150 cc /hour is safe and effective when oral administration is not feasible Ammonium chloride poisoning is itself a hazard and is particularly likely in patients with renal disease who are receiving ammonium chloride It is manifest by azotemia hyperchloremic acidosis and coma and is treated when necessary by administration of large quantities of sodium lactate or bicarbonate For patients unable to tolerate ammonium chloride given orally dilute hydrochloric acid is a satisfactory substitute

The low salt syndrome is specifically distinct from hypochloremic acidosis in which serum sodium content is normal Hyponatremia during congestive heart failure may result from salt depletion or frequent paracenteses but often occurs without obvious cause In cases of true sodium depletion replacement by a slow infusion of 200 300 cc of 5% sodium chloride daily for two or three days is indicated Patients with this syndrome with no apparent salt depletion have a poor prognosis and do not respond well

Potassium depletion is uncommon in congestive heart failure but may be produced by mercurials or ammonium chloride The digitalis toxicity often evident after mercurial diuresis is probably due to potassium loss Not only potassium but also calcium may become depleted following use of cation exchange resins hyperchloremic acidosis may supervene as a result of retention of hydrogen or ammonium in place of sodium Carbonic anhydrase inhibitors by increasing renal excretion of bicarbonate may also produce hyperchloremic acidosis

(1) J A M A 154 1 37 1241 Apr 10 1954

in those with a small myocardial reserve It is important also to recognize that small doses of digitalis have no effect what ever and a minimal concentration must be present in the body for the drug to influence the heart favorably

Carotid sinus hypersensitivity may be increased by digi talis toxicity Other neurologic complications include different vagal disturbances and convulsions Idiosyncrasy to digitalis is extremely rare

Observations on Pathogenesis of Congestive Failure in the experimental animal are reported by A Clifford Barger A M Rudolph and E F Yates[9] (Harvard Med School) Chronic right sided failure was produced in dogs by a combination of tricuspid insufficiency and pulmonary stenosis Sodium excre tion studies were done on these animals and also on dogs with less severe valvular damage Isotonic saline (500 ml) was given intravenously before operation as a control two weeks after production of tricuspid insufficiency and after develop ment of frank congestive failure when pulmonary stenosis was superimposed In the control experiment about 40% of the sodium chloride and water load was excreted in the first hour After tricuspid insufficiency was produced with elevation of resting right atrial pressure but normal exercise tolerance only 10% of the sodium chloride and water was excreted in the first hour After imposition of the pulmonary lesion and de velopment of congestive failure only 0 5% of the infused sodium in eight hours but 15% of infused water was excreted This suggests dissociation of excretory function In another experiment a similar result followed oral salt water loading

To determine what effect elevated venous pressure had observations were made on a dog with isolated pulmonary insufficiency with no elevation of venous pressure Here again there was delay in sodium excretion Moderate pul monary stenosis producing elevation of right atrial pressure did not detectably alter sodium elimination thus establishing the fact that elevated venous pressure is not a sufficient ex planation for the derangement

Studies on other animals utilizing endogenous creatinine clearance as a measure of glomerular filtration rate indicate that the site of the altered physiology is in a greatly in creased tubular reabsorption of sodium demonstrable during constancy of the filtered sodium load

(9) B ll New F gland M C ter 16 24 29 M h 1954

centrations of serum sodium hypertonic saline should be given cautiously according to the patient s response

Bedside Method for Determining Serum Chlorides as Aid in Detecting Chloride Depletion Syndrome in Patients Receiving Mercurial Diuretics A striking feature of diuresis with mercurial diuretics is profuse excretion of urinary chlorides and lowering of plasma chloride levels With prolonged mercurial diuresis hypochloremia characteristically develops When plasma chlorides fall to a low level—85 mEq or less—mercurial diuretics are ineffective if not dangerous

As a guide to mercurial diuresis the pattern of urinary chloride excretion is easier to follow and a much more sensitive indicator of chloride depletion than fluctuations of chloride concentration in the blood Significant changes are observed in the plasma chloride concentration only after the depletion period becomes profound In the estimation of chloride depletion in patients receiving mercurial diuretics undue reliance should therefore not be placed on serum chloride values unless they are definitely low Li Tsi Gziou and Jacob J Silverman[3] (Staten Island N Y) present a simple rapid bedside method of measuring serum chloride level that compares favorably with the standard Schales and Schales mercurimetric method without use of complicated equipment

METHOD —A kit containing a test tube a dropper a 10% solution of potassium chromate and a 0 73% solution of silver nitrate constitutes all the necessary equipment Five to 10 cc blood obtained from any convenient venipuncture site is allowed to clot in a test tube To exactly 10 drops of erum obtained from this specimen 1 drop of the potassium chromate solution i added A yellow orange color is produced The silver nitrate solution is added drop by drop the number counted until a reddish brown color is produced after the mixture is gently shaken This end point is easily discernible Each drop of silver nitrate solution required to produce this end point represents 15 mg /chloride/100 cc serum The average normal patient will require between 23 drops (equivalent to 345 mg chloride expressed as 575 mg sodium chloride/100 cc) and 25 drops (equivalent to 375 mg chloride expressed a 625 mg sodium chloride/100 cc) To check the results the procedure is repeated with 20 drops of serum The value obtained should be exactly double

Critical Analysis of Cation Exchange Therapy A G Spencer and H G L Lloyd Thomas[4] (Univ College London) studied 39 patients with peripheral edema of whom 9

(3) Am J M S 225 5 1 5 4 M y 1953
(4) B t M J 1 597 603 M 13 1954

Low Sodium Syndrome Its Origins and Varieties Hypo natremia may result from sodium depletion and dilution There is also a third category of chronic hyponatremia associated with prolonged malnutrition The primary disturbance seems to lie in the nutritional intracellular depletion and hypo osmolarity with hyponatremia being a compensatory adjustment In both the clinical and the experimental low sodium state certain observations stand out impaired water diuresis decreased excretion of sodium in urine sweat saliva and gastrointestinal secretion early decrease in cardiac output with little fall in blood pressure reduction in renal blood flow and glomerular filtration rate increased tubular reabsorption of sodium and refractoriness to mercurial diuretics Some of these changes point to increased secretion of antidiuretic hormone (ADH) and adrenal cortical salt retaining hormones The combined effect is to promote sodium and water retention apparently to preserve the volume of extracellular fluids Since sodium is usually not available and water is excessive water retention occurs and causes dilution of body sodium Louis Leiter Raymond E Weston and Jacob Grossman (Montefiore Hosp New York City) believe that in certain circumstances volume regulation takes precedence over hypothalamic osmoreceptors and ADH secretion is increased instead of shut off

Treatment of the low sodium syndrome depends largely on whether it is due to depletion or dilution The physician must review the pathologic and/or therapeutic mechanisms which induced the defect In congestive heart failure there appears to be increased ADH secretion leading to water retention and sodium dilution compounded with this may be the sodium depleting effects of a low salt diet and mercurial diuretics Prolonged loss of gastrointestinal secretions may be complicated by intravenous infusions of salt poor solutions which contribute to sodium dilution

Treatment of the edematous patient may present special problems in the interpretation of whether sodium depletion or dilution plays the major role The authors recommend with *holding* saline unless the serum sodium level is very low—115 mEq /l or less—or there has been a rapid fall in serum sodium value with no gain in weight At extremely low con

(2) B ll N w Y k A d M d 29 833 845 N emb 1953

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(3) Am J M S 225 5 1 524 M y 1953
(4) B i M J 1 597 603 M 13 1954

had renal disease and 30 cardiac disease The patients were given a sulfonated polystyrene resin administered as a 3 1 mixture of the ammonium and potassium phases except four who were given hydrogen phase resin and four given a mixed cation anion exchanger 29% in the potassium phase The usual dose was 20 Gm three times daily for two to eight weeks The patients were at bed rest and on a low salt (11 23 mEq /day) and restricted fluid diet

Considerable improvement was noted in 55% of the patients Poor results were obtained in those with chronic congestive cardiac and renal failure and in patients with a plasma sodium level below 130 mEq /L On the same diet fecal excretion of sodium varied widely from one patient to another although it was fairly constant for each individual Fecal elimination of sodium was decreased by increasing dietary intake of potassium and gradually declined as the total body sodium was decreased There was no clinical evidence of calcium depletion Hyperchloremic acidosis was noted in six patients with renal disease but was less apparent in the four with renal disease treated with a mixed anion cation exchanger

Although not recommended for general treatment of edema resins are valuable in persistent congestive heart failure *when edema is unresponsive to other measures* when mercury or digitalis is contraindicated or inefficacious and as prophylaxis against recurrence of edema during convalescence from heart failure An excellent response is also obtainable in type II nephritis and in early diabetic nephrosclerosis in the absence of azotemia

Resins are contraindicated in gastrointestinal disorders renal failure cation depletion and advanced liver disease

Ingestion of resins allows but little increase in intake of sodium *There is good evidence that resins extract* sodium from body fluids Ingestion of 1 pt milk daily tends to prevent calcium and magnesium depletion Concurrent administration of potassium as the citrate or in fruit juice is beneficial Digitalis intoxication may occur when serum potassium level is lowered by resin therapy

Venesection in Treatment of Congestive Heart Failure, Erythremia, Aortic Aneurysm and Hemochromatosis Joseph K Bradford, William Arrowsmith W D D..

Thomas Findley (Tulane Univ) feel that judicious blood letting has a rational place in these four conditions

Although few dispute the value of phlebotomy in acute pulmonary edema its place in congestive heart failure of other origin is not well established Patients with chronic cor pulmonale and right ventricular failure are often benefited by measures which reduce blood volume and venous pressure

In the management of polycythemia vera (erythremia) irradiation especially by radioactive phosphorus has become the treatment of choice Phlebotomy serves only to stimulate bone marrow activity whereas irradiation depresses it However venesection should be used for quick relief of symptoms or during the latent period before radioactive materials exert their full inhibitory force The end point of venesection is satisfactory reduction of red blood cell volume When used alone this may require the removal of several liters of blood over a period of days or weeks the normal red blood cell volume can often be stabilized by withdrawal of 500 ml every few weeks or months

Venesection and withdrawal of sufficient blood to produce severe anemia has been successfully employed for many years in treatment of aortic aneurysm For example in a man 57 who had a thoracic aneurysm pushing out through the sternum multiple venesections caused disappearance of the mass and he was asymptomatic 14 years later The authors treated 10 patients in this way 7 successfully They removed 500 ml daily or every other day until hemoglobin content was reduced to 6 Gm /100 ml Five of the successfully treated patients were observed for two years in none was the aneurysmal sac reduced in size but relief of symptoms was striking

Hemochromatosis responds well to massive venesection inasmuch as the fundamental defect appears to be undue uptake of ingested iron which is trapped in the body The authors generally bleed the patients at a rate of 2 4 L /month with reinjection of the separated plasma after every venesection to minimize protein loss Serial liver biopsies of one patient showed diminution of iron stores and return to nonpigment bearing liver

Role of l Nor Epinephrine in Treatment of Shock is evaluated by Louis Sokoloff Benton D King and Richard L Wechsler[6] (Univ of Pennsylvania) The ideal adjuvant agent

(5) P stg d Med 14 403 409 N mb 1953
(6) M Cl N th Am 38 499 514 M h 19 4

in treatment of severe shock should so far as possible cause a vasoconstrictor pattern similar to that produced by circulatory reflexes in the intact body i e it must favor blood flow to the vital organs Second it should constrict capillaries and venules since stasis in these vessels often occurs in shock The agent should not increase metabolism have no toxic effects be easily administered intravenously and be controllable with ease

Nor epinephrine satisfies many of these requirements Although experimentally it has been shown to reduce cerebral blood flow in normotensive persons there is indirect clinical evidence (by appraisal of level of consciousness) that in decompensated shock cerebral oxygenation is somehow improved Unlike epinephrine it has no direct stimulatory effect on the brain It increases diastolic blood pressure but does not increase the heart rate or cardiac output having no direct action on the heart Total peripheral vascular resistance is increased but cerebral and total body oxygen consumption are not elevated (except as noted) and the pituitary adrenal axis is not stimulated In all these actions it differs significantly from its methylated analogue epinephrine

The only practical method of administration is by continuous intravenous infusion since the action of a single intravenous dose is too fleeting and the effects of an intramuscular dose too delayed and unpredictable The most commonly used solution is one containing 4 μg/ml Vehicles may be glucose in water or saline isotonic saline plasma substitutes plasma or whole blood Rate of administration depends on the patient s condition and response elicited The dose should be merely enough to produce the effect desired When necessary concentrations up to 32 μg/ml can be used Plastic catheters should be used in the arms since venospasm or tissue sloughs are more prone to occur in the legs

The drug appears to be particularly valuable in shock following myocardial infarction It does not seem to contribute to the danger of pulmonary edema Although serious arrhythmias in the unsensitized heart have not been reported the drug probably should not be used during cyclopropane trichlorethylene or chloroform anesthesia

[Patients with the clinical picture of shock as a result of myocardial infarction frequently display a dramatic response to the slow intravenous administration of a rapidly acting preparation of digitalis such

as lanatoside C This may be combined with intravenous infusion of nor epinephrine Although the nor-epinephrine tends to increase the work of the heart, the clinical improvement which usually occurs in these circumstances suggests that the coronary blood flow is even more in creased. These two procedures are the treatment of choice for a shock like state complicating myocardial infarction —Ed]

Nor Epinephrine in Shock Following Myocardial Infarction Influence on Survival Rate and Renal Function. John J Sampson and Albert Zipser[7] (Mount Zion Hosp San Francisco) report results of nor-epinephrine therapy in 30 patients with shock associated with myocardial infarction 14 had had recurrent episodes of hypotension and 16 had been in shock for over an hour or were in severe shock Although these patients were relatively poor risks 20 patients survived the episode of shock 16 recovered clinically and were discharged from the hospital

Nor epinephrine was given in 5% aqueous solution of glucose in doses of 1 5 150 μg /minute Blood pressure was maintained at about 100 mm Hg systolic unless the patient had been hypertensive when levels of 110-125 mm were sought When therapy was prolonged maintenance of adequate urine flow was an added criterion of response In three patients p aminohippuric acid and endogenous creatinine clearances were measured Although glomerular filtration rate did not change from its low base level (30-68 ml /minute) renal plasma flow as measured by p aminohippuric acid was depressed but after cessation of therapy it increased from 28 to 42%

Congestive heart failure did not increase in any case although one of the effects of nor epinephrine is to increase cardiac work One patient with complete heart block required as much as 150 μg nor epinephrine/minute to maintain satisfactory blood pressure Ventricular tachycardia developed which was controlled with quinidine

Venospasm phlebitis and localized tissue necrosis had no apparent influence on recovery

The continuous administration of this pressor agent with attendant high percentage of recovery suggests a modification of previous concepts of irreversible shock The artificial maintenance of blood pressures apparently permits the organism to survive a critical period until the natural mechanisms for maintaining the blood pressure are resumed The restitu

(7) C cul t 9 38-47 J ry 1954

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(7) C cul t on 9 38 47 J ry 1954

tion was more often abrupt than gradual and occurred from several hours to 5½ days after therapy was started

Nor-Epinephrine Effect in Normal Subjects, Use in Treatment of Shock Unresponsive to Other Measures To prevent the hypotensive patient from slipping into the so called irreversible phase of shock an agent is desirable which will consistently raise the blood pressure and hence the per fusion pressure of the brain kidneys and other vital organs Such an agent should operate independently of the derange ment which generated the hypotension its effects should be easily controlled and of short duration permitting abrupt termination if necessary and side effects should be minimal Nor epinephrine meets most of these criteria John H Moyer James M Skelton and Lewis C Mills[8] (Baylor Univ) dis cuss the pharmacology and clinical application of this com pound

Twenty *normal subjects each received a single* subcu taneous injection of nor epinephrine (average 6γ/kg) and five were given the drug by continuous intravenous infusion (4 mg /L of 5% glucose in distilled water) Subcutaneous injection caused a vasopressor effect in 1 5 minutes which lasted 15 60 minutes In these subjects the diastolic blood pressure increased equal to or more than the systolic the pulse rate was consistently decreased (average 23%) average hematocrit reading increased 12 5% Respiration vital capac ity or concentration of blood glucose did not change Those given the drug intravenously had an immediate pressor re sponse which lasted about a minute after discontinuance The bradycardia could be blocked with atropine without affecting the blood pressure

After administration of the preparation three subjects showed definite changes in rhythm on the ECG consisting of a shift in the site of the pacemaker to another auricular site nodal or auricular premature contractions and heart block One subject showed a Wenckebach phenomenon All of these changes were transient and returned to normal about the time the pressure returned to the control level No ventricular pre mature *contractions were noted*

Of 44 patients with shock who were given constant intra venous infusion of the same concentration of nor epinephrine

(8) Am J Med. 15 330 343 S pt mbe 1953

only 2 failed to show a pressor response Some had previously failed to respond to adequate fluid replacement and blood transfusions The concentration of nor epinephrine was increased to 24 mg /L in less responsive patients Blood pressure level was regulated by rate of infusion Etiologies of shock were myocardial infarction overwhelming infection antihypertensive drugs hemorrhage transfusion reaction and trauma Nor epinephrine was considered particularly beneficial for patients with normal or increased blood volume if further administration of intravenous fluid was contraindicated or ineffective It was also valuable in counteracting inordinate response to hypotensive drugs

Nor epinephrine is of limited value in the treatment of shock associated with severe infection or any other disease unless the primary cause of the shock is corrected as much as possible Since the effect of nor epinephrine is predominantly on the arterioles and there is no significant increase in cardiac output with little or no increase in myocardial irritability if used cautiously the authors recommend its use in treatment of shock secondary to myocardial infarction They suggest the concurrent use of quinidine and nor epinephrine Except for a decrease in heart rate there were no electrocardiographic changes attributable to nor epinephrine

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ELECTROCARDIOGRAPHY

Studies on Mechanism of Ventricular Activity—*VI Depolarization complex in pure subendocardial infarction role of subendocardial region in normal electrocardiogram*—Activation of the subendocardial layers has been thought to cause the initial portion of the normal R wave in surface and precordial leads and a subendocardial infarction has been considered to cause an initial abnormal Q

Myron Prinzmetal Clinton McK Shaw Jr Morton H Maxwell Eileen J Flamm Alfred Goldman Noboru Kimura Louis Rakita Jean Louis Borduas Sol Rothman and Rexford Kennamer[9] (Los Angeles) studied 7 dogs with chronic subendocardial infarcts produced by coronary artery ligitation and 12 dogs with acute subendocardial electrocoagulation

(9) Am J M d 16 469-489 Ap 1 1954

burns with necrosis by means of epicardial intramural and cavity ECG leads and subsequently pathologic examination In no instance of chronic infarction did the epicardial leads register abnormal Q waves and in six the deflections were entirely normal In the exception small R waves were present which were probably lower than in the control leads Intra mural tracings recorded over and within the infarcted areas appeared normal

No Q wave was apparent in surface leads over the electro coagulation subendocardial infarct in 10 dogs Small Q waves present before injury in 2 dogs became deeper and broader but remained within normal limits

Approximately the inner two thirds of the normal ven tricular wall appears to be electrocardiographically silent and the normal ECG results from activation of the outer lay ers of the heart Unipolar intramural leads recorded through out the inner ventricular layers of the normal dog heart showed QS waves Tracings from the outer ventricular layers showed RS waves and as the electrode approached the epicardial surface the width and amplitude of the R wave increased Thus it is shown that the R wave recorded over normal hearts represents outer ventricular wall depolarization and is not significantly affected by subendocardial depolarization Approximate rates of intramural depolarization were meas ured with cathode ray oscillograms It was estimated that depolarization of the inner ventricular layers occurred at a rate approximating several thousand millimeters per second whereas the outer layers depolarized at about 300 500 mm/ second Subendocardial depolarization may fail to affect the ECG because it occurs too rapidly to be recorded and conse quently pure subendocardial infarcts do not significantly alter the depolarization complex

[These and the following study with the previous publications by the same group probably constitute a landmark in the whole field of electrocardiography The evidence presented appears to be overwhelm i gly strong that the QRS complex as recorded by the usual clinical technics is affected only by the subepicardial musculature The imme diate implications for electrocardiographic theory and the long range im plications for practical interpretation of the electrocardiogram are obvious —Ed]

VII Origin of coronary QR wave—Since they previously showed that subendocardial lesions did not cause QR waves in dogs Shaw Goldman Kennamer Kimura Inga Lindgren

Maxwell and Prinzmetal[1] undertook to determine in what circumstances the coronary QR wave does occur Myocardial infarctions were produced in dogs by ligation of the anterior coronary artery and 23 infarcts were studied which showed 26 well defined QR waves (three being registered on two leads each)

Histologic examination of the myocardium under the lead point in each and gross pathologic inspection of the heart were correlated with ECG findings In every instance the QR lead point was located near or directly over dead muscle In 21 of the 23 ventricles QR waves were recorded at or near the edges of transmural infarcts while QS waves appeared over the center four transmural infarcts of a patchy type with a speckled appearance characteristic of mixtures of live and dead tissue demonstrated QR waves over the center as well as over the edges Examination of the subendocardial area subtending each epicardial QR lead point showed it to be dead partially dead or completely normal thus making it evident that the coronary QR waves could not be correlated with the gross or microscopic appearance of the inner ventricular layers The only histologic feature common to all 25 QR regions was the presence of both viable and dead muscle at superficial levels in or near the QR regions This conclusion was strengthened by demonstration of injury currents occurring when pressure was applied to the QR lead points

Death of outer ventricular muscle after coronary artery occlusion eliminates or reduces the magnitude of the R wave and negative potentials (Q or S waves) transmitted through the dead subepicardial muscle further alter the depolarization complex Thus a mixture of live and dead muscle in the outer ventricular layers may result in a variety of QRS changes depending on the relative magnitude and timing of the reduced positive epicardial potential and the transmitted negative potential

Effect of Cooling Anterior Chest Wall on the T Wave of the Electrocardiogram was studied by S A Rahman R N Abhyankar and Tahir Ali (Hyderabad India) and the results compared with those obtained by other investigators after ingestion of ice water A bag of crushed ice was placed

(1) Am J Med 16 490 503 Ap 1 1954
(2) Am H t J 47 394 404 M h 1954

on the chest of the subject for 5 minutes and the six bipolar leads and $V_{1\ 4}$ V_6 and V_8 were taken Such cooling of the pre cordial region depressed (decreased positivity or increased negativity) the T wave in leads $V_{1\ 4}$ The change was less pronounced in subjects in good nutritional state with thick chest wall Although in certain subjects the blood pressure became elevated this could not be correlated with T wave change An ice bag on the abdomen failed to produce ECG changes which would tend to exclude chemical neural or humoral mechanisms activated by the stress itself and would implicate direct cooling of the anterior wall of the heart

The T wave changes resulting from cooling of the chest wall were in the main opposite those produced by drinking ice water which is assumed to cool the posteroinferior surface of the heart Changes were not accompanied by change in the shape or size of the QRS The ventricular gradient had a slight tendency to move to the left These primary T wave changes are assumed to be caused by delayed repolarization of the epicardial surface of the anterior heart wall resulting from actual cooling of the surface of the heart

Relation of Age to Certain Electrocardiographic Responses of Normal Adults to Standardized Exercise is documented by Harold M Silver and Milton Landowne[3] (Nat l Inst of Health) after study of 60 men rigidly screened for evidence of cardiac disease and divided into three age groups 20 39 40 59 and 60 79 years The two step test was modified to provide for total work of 600 kg m total work/sq m body surface in three minutes Records were made before imme diately and at 2 4 6 and 10 minutes after completion of exercise

The mean cycle length (R R) for each age group was nearly the same before exercise and decreased equally after 2½ minutes of exercise Recovery was slower in the old group The S T and T values in the resting state were within normal limits but after exercise there was greater depression of the S T and decrease in T with age The decrease in T wave height tended to become maximal during the course of recov ery and occurred later in the old group with restoration of the normal repolarization pattern significantly delayed The oldest group had the greatest reduction in Q T interval during and immediately after exercise

(3) C rc lat on 8 510 520 Oct b r 195:

Correlation of Changes in Body Weight with Electrocardiographic Pattern Arnold H Kadish[4] (Beverly Hills Calif) reports on four overweight patients aged 42 70 whose ECG abnormalities varied with their weight One had probable angina pectoris but none had a history of myocardial infarction The ECG abnormalities consisted of T wave changes including inversion in leads I and V_6 in all but one case No S T segment changes were reported There was a return of normal pattern in all cases with loss of as little as 9 lb In two patients believed to have coronary disease T wave abnormalities returned with gain in weight Although isolated T wave inversion in itself has no practical significance the correlation of abnormalities with loss and gain of weight in these patients is suggestive of increased cardiac strain with obesity

Electrocardiograms in Anemia V V Shah (Bombay) reports ECG studies of 20 patients with anemia but without associated diseases likely to give rise to ECG changes Nearly all were young and all had hemoglobin values 10 30% of normal Eleven had cardiac enlargement

Sinus tachycardia was present in most although two had sinus bradycardia The combined voltage of the QRS complexes in unipolar or bipolar limb leads was less than 15 mm in 13 cases and within normal limits in 7 The T wave was biphasic or inverted in nine abnormally low in seven and normal in only four (who incidentally had severe anemia) In five cases the S T segment was abnormally depressed in multiple leads

In the patients who were followed with serial ECG s during treatment for anemia the abnormalities regressed Cardiac size likewise was reduced in some

Electrocardiographic Pattern Simulating Acute Myocardial Injury and resembling anteroseptal damage with right bundle branch block was observed in three healthy subjects by Harold L Osher (Portland Me) and Louis Wolff[6] (Boston)

The normally isoelectric S T segment represents the interval when depolarization has been completed and the potentials associated with repolarization have not attained sufficient magnitude to be registered The latter are expressed in the T

(4) Am P t 4 513 538 A g t 1953
(5) I dia H art J 4 329 356 S pt mber 1953
(6) Am J M S 6 341 545 N ember 1953

wave By the time the depolarization process has reached the last regions of the ventricles if repolarization of regions activated earlier is sufficiently advanced to produce significant potentials deviation of the S T segment will occur This is seen in tachycardia and in intraventricular conduction disturbances In the latter conditions the S T segments and T *waves are deviated in the direction opposite that of the main* deflection of QRS Myocardial injury classically produces elevation and upward bowing of the S T segment and pointed symmetrical inversion of the T wave i e the S T segment and T wave are deviated in opposite directions

The tracings had the following characteristics (1) QRS interval was prolonged or at the upper limit of normal (2) There were small R moderate or deep S and prominent wide R deflections in the right precordial leads and broad S waves in the I and left precordial leads the typical configuration of right bundle branch block (3) The R deflections merged imperceptibly with the ST T complex in a smooth sometimes coved descending line so that it is difficult to locate the junction of QRS and S T (4) Right precordial T waves were inverted or diphasic (5) The pattern was constant or showed only minor variations in serial tracings Such a pattern differs from the usual right bundle branch block pattern in that the S T segments and T waves are deviated in opposite directions It resembles the pattern resulting from acute injury but fails to undergo the usual process of evolution

This pattern may result from overlapping of ventricular activation and recovery with simultaneous recording of potentials due to depolarization and repolarization with fusion of the terminal portion of the QRS complex and the initial portion of the ST T complex This is apparently due to prolongation of the depolarization process by right bundle branch block

Value of Additional Thoracic and Abdominal Unipolar Leads for Diagnosis of Location and Extension of Myocardial Infarctions The 12 routine ECG leads often do not indicate the extension of lateral infarctions or provide unequivocal evidence of posterior or inferior infarcts Joseph Lambert (Spa Belgium) studied ECG findings in 88 patients with myocardial infarction and 33 normal persons in whom the usual

(7) Am Heart J 47 40 57 J n y 1954

12 leads were obtained and in addition V_7 V_8 and V_9 and three midline abdominal leads—V_E from the ensiform cartilage V_O from the umbilicus and V_{EO} from a point midway between the two The infarctions were of varying ages

From this survey it was concluded that lead V_E shows direct infarction patterns in nearly all anterior infarcts studied and in antero and posteroseptal infarcts It does not register changes in anterolateral and posterior infarcts but may show direct patterns when the infarcts become posterolateral Leads V_{EO} and V_O usually show direct patterns in *posterior infarcts (which are not registered by the V_E lead)* and in posterolateral infarcts In the latter these leads are more characteristic than V_E Leads V_{EO} and V_O are often silent in anterior anteroseptal and anterolateral infarctions Leads V_7 V_8 and V_9 may be useful for measuring the extent of a large anterior or anterolateral infarct and show direct infarction patterns in posterior and posterolateral necrosis

Thus by leading from V_E V_{EO} and V_O it is possible to learn whether a posterior infarct involves chiefly the inferior wall of the heart (V_{EO} and V_O) or spreads to the anterior wall (V_E) and reciprocally if an anterior infarct shown in V_E spreads over the inferior wall and registers on V_{EO} and V_O Lead V_E seems to belong to the group of leads which explore the anterior wall of the left ventricle and septum Leads V_{EO} and V_O show the posterior or inferior wall and V_7 V_8 and V_9 explore the posterior and posterolateral walls of the left ventricle

Study of Unipolar Left Back Leads and Their Application to Posterior Myocardial Infarction was made by Stephen R Elek Lawrence M Herman and George C Griffith[8] (Univ of Southern California) Vertical lines were drawn in the posterior axillary line the posterior projection of the anterior midclavicular line (scapular or Sc line) and the spinous (Sp) line drawn 2 cm to the left of the thoracolumbar vertebral spines Points were marked for electrode placement where these three lines intersected horizontal lines which passed through the spines of thoracic vertebrae 2 4 6 8 10 and 12 and lumbar vertebra 2 The subjects generally prone while back leads were taken included 52 normal individuals 18

(8) C J t 7 656 668 M y 1953

patients with left ventricular hypertrophy 6 with right ventricular hypertrophy and 36 with posterior wall infarction

The most consistent findings in normal subjects were (1) epicardial complexes in all posterior axillary leads (2) epicardial complexes at or below Sp_4 and Sc_4 in subjects with heart in horizontal position and (3) tendency of the Q wave to become smaller at caudal levels along either line With the heart in other positions transitions from endo to epicardial complexes were found along the Sc and Sp lines at variable but recognizable levels In patients with right and left ventricular hypertrophy changes similar to those seen in conventional leads were recorded in the back leads

In all cases of posterior myocardial infarction established clinically and by conventional ECG leads the back leads also showed the infarct In addition back leads showed the transition from the septal Q to the infarct Q thereby allowing some estimation of size of the infarct In some patients clinically suspected of having myocardial infarction if conventional leads did not clearly demonstrate the infarct the left back leads offered specific evidence of infarction

Progressive deepening of the Q wave as the lower left back leads are recorded may indicate myocardial infarction just as well as the accepted criteria for an abnormal Q wave in lead aV_F Thus the significance of questionable Q waves in aV_F can be better evaluated by means of the left back leads Back leads may substitute for esophageal leads and are easier to take

Effect of Induced Hyperkalemia on Normal and Abnormal Electrocardiogram patterns was studied by Harold T Dodge Robert P Grant and Paul W Seavey[9] (Nat l Inst of Health) with particular reference to effects on the spatial T vector At least 15 Gm potassium chloride was given to each of 10 normal young men and several patients representing seven recognized types of T wave abnormality Results derived from previous studies in other laboratories were incorporated when the methods used were comparable Serum sodium potassium and hematocrit values were determined before and after potassium administration in many cases

In the normal subjects the ECG tracing showed increased

(9) Am Hea t J 45 725 739 May 1953

magnitude of the mean spatial T vector without significant change in its direction and a constant angle formed by the QRS and T vectors No significant alterations in S T segments or duration of Q T interval were observed

In three groups of patients the T vector abnormalities were caused by myocardial infarction left ventricular strain and left ventricular ischemia Within the category of left ventricular strain the authors include those with a QRS T angle of nearly 180 degrees and a definite S T vector that is relatively parallel with the T vector Patients with left ventricular ischemia had a normal QRS loop an abnormally directed mean spatial T vector pointing away from the left ventricle (and therefore an abnormally wide QRS T angle usually of 90 100 degrees) absence of a measurable S T vector In all patients potassium intake caused a change in magnitude of the T vector without return to normal of the QRS T angle

Patients with metabolic T wave abnormalities have a normal QRS loop no S T vector and an abnormally small or abnormally directed mean T vector or both The ECG pattern resembles that in left ventricular ischemia but these patients have no other evidence of heart disease In these patients potassium intake caused an increase in magnitude of the mean spatial T vector and a change in direction so that the QRS T angle became perfectly normal for a few hours In patients with localized areas of T negativity the area of isolated T deformity was never eliminated after potassium administration

The T wave abnormalities noted in normal subjects on tilting of the body were prevented when potassium was administered before the ECG recording Digitalis has been found to enhance the changes due to tilting Potassium increased the amplitude of the T vector which had been reduced by digitoxin and partially or completely prevented the digitalis induced tilt rotation of the T vector

Nearly all persons given potassium salt orally had gastric irritation and about half had mild signs of potassium intoxication One patient died of ventricular fibrillation after ingestion of 15 0 Gm potassium chloride

ARRHYTHMIAS

Emergency Treatment of Cardiac Arrhythmias Myron Prinzmetal and Rexford Kennamer[1] (Los Angeles) state that most arrhythmias can be controlled by rapidly acting digitalis preparations quinidine procaine amide carotid sinus stimulation and sedation Lanatoside G and ouabain are useful digitalis preparations When used orally or intramuscularly quinidine *is given every two hours for five doses then the individual* dose is increased if necessary Quinidine lactate prepared as 0 65 Gm quinidine in 50 150 cc of 5% glucose may be given intravenously at a rate of 2 cc/minute with relative safety Procaine amide may be given orally intramuscularly or intravenously in doses of 250 500 mg repeated in two hours Carotid sinus stimulation is best done by firm up and down strokes one side at a time

Paroxysmal auricular tachycardia often can be terminated by carotid sinus massage Elderly patients with rapid auricular tachycardia should be treated with digitalis and quinidine intramuscularly In infants this condition may cause congestive failure and requires immediate treatment with digitalis intravenously In auricular flutter or fibrillation slowing of the ventricular rate is imperative This can generally be done with *digitalis Occasionally conversion to sinus rhythm with* quinidine or procaine amide or both may be advisable Ventricular tachycardia demands prompt and vigorous therapy Treatment of choice is parenteral administration of quinidine or procaine amide or both

Epinephrine isopropylarterenol hydrochloride (isuprel®) and hydroxyamphetamine hydrobromide (paredine®) may be useful in preventing syncope in patients with complete heart block or carotid sinus hypersensitivity Quinidine and procaine amide are contraindicated in heart block but may be used to control paroxysmal ventricular fibrillation in patients with previously normal auriculoventricular conduction Cardiac massage and electric defibrillation are used in the treatment of cardiac asystole from standstill or fibrillation

The authors report a case in which heart block following

(1) J A M.A 154 1049 1054 M 27 1954

myocardial infarction presumed to be due to inflammatory tissue around the auriculoventricular node and the bundle of His was successfully treated with corticotropin

Treatment of Cardiac Arrhythmias is discussed by David Scherf (New York Med College) with emphasis on controversial points Therapy chiefly centers on quinidine digitalis vagotonic agents and procaine amide Not every arrhythmia needs to be treated The cardinal principle of *primum non nocere* is too often ignored

The efficacy of quinidine can be correlated with the blood concentration Levels over 10 mg /L are occasionally necessary and are often associated with toxic effects Administration every two hours for five doses or every four hours around the clock is recommended in an attempt to break the arrhythmia Administration should be stopped if extrasystoles appear or if duration of the QRS complex equals 0 11 second or more The vagolytic and sympathicolytic effects of this agent are often not appreciated the drug negates the effect of carotid pressure and may also produce vasodilatation

Digitalis readily abolishes extrasystoles and tachycardias and prolongs A V conduction However it is prone to increase ventricular irritability and the appearance of variform ventricular extrasystoles or tachycardia with A V block are manifestations of overdosage

Procaine amide acts as quinidine and may often be substituted for it Many instances of hypersensitivity to the drug have been reported Intravenous administration of this drug as well as of quinidine is dangerous and is only rarely indicated

Low intracellular potassium may be a causal factor in the propensity of diseased myocardium to develop tachysystolic centers Potassium may be given but with great care Barbiturates distinctly reduce the tendency of the heart to develop arrhythmias

Variform ventricular extrasystoles denote organic heart disease and should be treated with quinidine Scherf strongly recommends the use of quinidine in every case of myocardial infarction with ventricular extrasystoles Paroxysmal tachycardias should first be treated with vagal stimuli Carotid pressure rather than massage should be used Scherf has

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(2) C l t on 8 756-768 Nov mbe 1953

abandoned the use of ocular pressure because retinal detachment has occurred twice Auricular fibrillation with a slow ventricular response need not always be treated Definite contraindications *to defibrillation exist in patients with mitral* stenosis and a large left auricle because of the danger of embolism Ventricular fibrillation is best treated with procaine hydrochloride and electric defibrillation Therapy of Stokes Adams attacks depends on the pathogenesis and cardiac arrhythmia present in the individual case

Treatment of Stokes Adams Disease by External Stimulation of Heart Paul M Zoll Arthur J Linenthal and Leona R Norman[3] (Harvard Med School) developed a cardiac pacemaker which transmits monophasic rounded electric impulses with an average duration of 2 3 msec between two electrodes placed on the surface of the chest the negative electrode being placed at the point of maximum cardiac impulse and the positive electrode symmetrically on the right anterior chest Frequency may be varied between 30 and 180/stimuli/minute with amplitude from 0 to 150 volts

The instrument was used on 14 patients with recent Stokes Adams attacks 11 of whom were treated for periods up to 108 hours for resuscitation from syncope or for maintenance of adequate ventricular rhythm In two patients trial stimulation produced effective beats but prolonged treatment did not become necessary Efficacy of stimulation was not determined in the other patient In each case the threshold voltage of effective stimulus was determined Continuation of stimulation and its duration depended on frequency and severity of the syncope nature of spontaneous ventricular activity and tolerance of stimulation by the patient Prolonged treatment beyond the time of resuscitation is preferable when syncope is frequent or severe and ventricular rhythms unstable Paroxysms of irregular ventricular tachycardia or fibrillation were not stopped by stimulation When tachycardia stopped spontaneously however stimulation was immediately effective and shortened the period of subsequent standstill

The chief untoward effects were muscular twitching and chest pain External electric stimulation did not produce multiple ectopic ventricular beats or ventricular fibrillation Autopsies on five patients showed no evidence of damage from

(3) C cul t on 9 48 -493 Ap 1 1954

stimulation to the heart In eight patients death was clearly due to Stokes Adams attacks In three of these stimulation was not applied at all and in two was applied only after irreversible cerebral damage had occurred it was ineffective in three presumably because the attack was due to persistent irregular ventricular tachycardia

***Abnormal Rhythms Associated with Cardiac Surgery and* Their Treatment** are reviewed by J Scott Butterworth[4] (New York City) Virtually any cardiac arrhythmia may occur during cardiac surgery The most important aspect of treatment is accurate and immediate diagnosis followed by specific and immediate remedy Monitoring of the ECG is essential and an oscilloscope is useful in registering a continuous visual tracing which can be transposed onto a direct writer if indicated The ECG can also be recorded on tape concurrent with visualization of the pattern on the oscilloscope Thus a permanent record is made which can be played back immediately if necessary The author monitors the ECG on an oscilloscope with an esophageal lead which he believes lends precision to diagnosis of the arrhythmia

Digitalis is given preoperatively only to patients who are already taking the drug or to those with chronic auricular fibrillation or flutter to control ventricular rate The same rationale is used with quinidine and pronestyl ® the drugs are withheld until specifically indicated Adequate oxygenation is necessary in handling sinus tachycardia or bradycardia Prostigmin® or tensilon® may be helpful in controlling tachycardia atropine may increase the rate of sinus bradycardia or the bradycardia of auricular fibrillation controlled by digitali Paroxysmal auricular fibrillation and flutter may be controlled by rapid digitalization or by pronestyl® given intravenously Pronestyl ® with pressor amines if necessary is the drug of choice for ventricular tachycardia Ventricular fibrillation is treated with immediate cardiac massage (if the chest is open) followed by passing of 60 cycle current through the heart at brief periods Calcium chloride or epinephrine may be injected directly into the heart Reports have been published of defibrillation of the heart through the unopened chest wall and the production of rhythmic stimulation and contraction of the heart by electrodes on the outside of the

(4) A I t M d 39 1088 1095 No mber 1953

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(3) C cul t 9 48 493 Ap 1 1954

auriculoventricular (A V) heart block (two each with 1st 2d and 3d degree heart block) Following intravenous administration of 5 10 mg banthine® ventricular rate increased 20 80 beats per minute and prolonged P R intervals were shortened from 0 40 to 0 60 second below premedication values Maximal action was observed 45 90 seconds after administration The hypertensive carotid sinus reflex was temporarily abolished in all six patients In the patients with complete heart block auricular rate was increased but ventricular rate unchanged

Banthine® was given orally to the six patients with cardioinhibitory carotid sinus syndrome and to a boy 10 with partial A V block who was subject to fainting spells The cardioaccelerator effect occurred 15 90 minutes after oral administration of 50 mg in five patients and lasted 3 6 hours In two patients followed four weeks syncopal episodes disappeared and no cardioinhibitory response to carotid sinus pressure could be elicited on a regimen of 100 mg banthine® daily A dose of 200 mg daily abolished the cardioinhibitory response in four additional patients One patient with a hypersensitive carotid sinus and associated Meniere s disease with right labyrinthitis continued to have dizziness and weakness and the cardioinhibitory effect of carotid sinus pressure persisted despite 400 mg banthine® daily

Six patients had side effects of dryness of the mouth pupil dilatation and weakness of the detrusor muscle with urinary retention which disappeared within two hours after oral administration of the drug One of two patients given probanthine® had erythema multiforme type skin eruption

Relatively large therapeutically effective doses of banthine® can be administered with fewer side effects than are observed with comparable doses of atropine

Multiple Episodes of Cardiac Arrest Report of Case is presented by Brooke Roberts Truman G Schnabel Jr and I S Ravdin[7] (Univ of Pennsylvania)

Woman 68 was hospitalized because of frequent diarrheal stools weight loss and for closure of a transverse loop colostomy done for diverticulitis She had had many sore throats as a child and 14 years previously had been treated with rest and digitalis for nerves Blood pressure was 140/84 There were a soft apical systolic murmur and a split mitral first sound Rhythm was regular

(7) J A M A 154 581 584 Feb 13 1954

body Cardiac arrest is treated with massage pressor amines and perhaps calcium injected into the heart Defibrillation is not indicated if the ECG does not show ventricular fibrillation

Control of Vagal Cardiovascular Reflexes during Surgery Employing Beta Diethylaminoethyl Xanthene 9 Carboxylate Methobromide (methantheline) Katherine Fisher and Travis Winsor[5] (Univ of Southern California) evaluated the effects of methantheline (banthine®) and digitoxin in 202 surgical patients of whom 194 had operations on or within the chest and 88 nonsurgical patients They were divided into four groups one receiving no medication except morphine scopolamine and secobarbital which were given to all one receiving 0 8 1 2 mg digitoxin orally 12 hours before surgery another given 50 100 mg methantheline bromide orally 1 2 hours preoperatively and the fourth group given both digitoxin and methantheline bromide Hypertension was noted in 83 patients who were approximately equally distributed in the four groups Patients receiving digitoxin and methantheline had fewer reactions than the controls and the patients receiving both drugs had still fewer vagal cardiovascular reactions Those receiving methantheline alone had fewer reactions than those taking digitoxin alone The effects of the drugs were particularly significant in hypertensive patients

Four other patients with digitalis intoxication were given methantheline bromide Loss of the conduction defect was noted in all together with reversion to sinus rhythm

Tests with other patients showed the drug to be ineffective in producing postural hypotension and in abolishing the Flack reflex (rise in systolic pressure after blowing against resistance) and unsuccessful in interrupting the cold pressor response Digital vasoconstrictor reflexes were inhibited to a moderate degree in four of seven patients

Methantheline bromide significantly reduces the incidence of vagal cardiovascular reflexes It is a powerful antagonist to the vagotonic effect of digitalis

Effect of Banthine® on Cardiac Mechanism in States Associated with Increased Vagal Tone Thomas Haymond and Samuel Bellet[6] (Philadelphia Gen l Hosp) treated six patients with cardioinhibitory carotid sinus syncope and six with

(5) A sthe ol gy 14 596 608 N mbe 1953
(6) Am J Med. 16 516 520 Ap l 1954

cotton and sending through the heart 0 1 second bursts of a 60 c 110 volt alternating current

Massage alone did not stop ventricular fibrillation although it prevented the usual deterioration from the early fine rapid type to the late slow coarse type and occasionally made a coarse fibrillation revert to the early type Epinephrine alone did not stop fibrillation although it altered the pattern to make the process fine and rapid Electric countershock was very effective in stopping ventricular fibrillation in both early and late stages and also when the heart was under the influence of procaine or epinephrine When countershock was applied after 30 seconds of fibrillation a co ordinated and competent ventricular beat promptly returned when applied after 5 minutes however fibrillation was stopped but the ventricular contractions were inadequate to maintain normal circulation

If fibrillating ventricles were continuously massaged then countershock applied a co ordinated and competent ventricular contraction immediately followed even when fibrillation had been present for 10 minutes Thus if fibrillation has been present more than 1 or 2 minutes cardiac massage should be used before application of countershock

Procaine injected into the ventricles slowed the rate of fibrillation or stopped it depending on the dose used However the rhythmicity of the heart was depressed and long periods of ventricular standstill occurred

If after five minutes of fibrillation epinephrine was administered before countershock competent ventricular contraction occurred similar to the results obtained by massage before countershock Fibrillation recurred frequently necessitating repeated use of countershock

Nature of Spontaneous Auricular Flutter in Man Report of Case Observed Directly during Cardiac Surgery The mechanism of spontaneous auricular flutter as it occurs in man has not been elucidated It has apparently been well established that the auricular flutter produced experimentally in animals can be the manifestation of a rapid circus movement in the auricles or more frequently of innumerable impulses radiating in all directions from a single ectopic auricular focus Myron Prinzmetal Alfred Coldman Eleanor Gerlach and Rexford Kennamer[9] (Univ of California Los An

(9) J A M A 153 553 555 Oct 10 1953

with a few extrasystoles Hemoglobin content was 55% on admission but was raised to 83% by transfusions

Intraperitoneal closure of colostomy was done under spinal anesthesia Suction drainage was continued for two days because of nausea Four days postoperatively she suddenly had a convulsion became apneic and pulseless Four minutes later heart beat was restored by a blow on the precordium Ephedrine was given to counteract hypotension The ECG showed auricular fibrillation and S T segment depression in all chest leads She recovered fairly well Five days later a similar episode occurred without convulsion Pulse and respiration were restored after five minutes by a blow on the chest Three days later cardiac arrest again occurred but she did not respond to previous measures Thoracotomy after 10 minutes of asystole showed the heart in ventricular fibrillation Regular rhythm was restored with massage and a defibrillator The next day she had a fourth attack The chest was opened three minutes after onset and one minute after cardiac massage was begun an effective beat returned Ventricular tachycardia supervened which responded to 0 4 mg atropine sulfate 0 5 Gm magnesium sulfate 100 mg procaine amide and 500 cc of a 1 2% solution of potassium chloride Rhythm was converted to a nodal beat Four days later another episode of asystole occurred and she died without further resuscitatory attempts

During the several postoperative days she had an elevated plasma carbon dioxide content and low plasma chloride and potassium levels which persisted until three days before death During the same time she received multiple injections of arterenol and procaine amide to combat hypotension and cardiac irritability respectively and whole blood and electrolyte solutions Quinidine was ineffectual in decreasing frequency of ventricular extrasystoles

Study of Usefulness and Limitations of Electric Countershock, Cardiac Massage, Epinephrine and Procaine in Cardiac Resuscitation from Ventricular Fibrillation Rene Wegria Charles W Frank Hsueh Hwa Wang George Misrahy Robert Miller and Peter Kornfeld[8] (Columbia Univ) induced fibrillation in 75 anesthetized dogs with minimal intensity alternating current applied to the exposed heart and investigated the efficacy of various methods in restoring effective contraction and blood pressure Cardiac massage consisted of rhythmic compression of both ventricles with one hand at a rate of 40 60/minute The descending aorta was compressed and partially constricted during massage to force more blood into the coronary and cerebral circulations Electric countershock was administered by enclosing the whole ventricular mass between two copper electrodes padded with saline soaked

(8) Ci culat n 8 1 14 J ly 1953

complicated by vascular collapse It is safe effective and acts rapidly There is no increase in cardiac irritability a decided advantage over phenylephrine (neo synephrine®) It does not increase the irritability of the cyclopropane sensitized heart unlike epinephrine arterenol and several other pressor amines It does not increase the ventricular rate of patients with heart block Methoxamine does not inhibit production of cardiac standstill by carotid sinus pressure In the normal subject with sinus rhythm methoxamine tends to produce bradycardia

Acetylcholine and the Heart Beat Acetylcholine stimulates skeletal muscle and might be expected to stimulate cardiac muscle which is also striated However the rate and force of the heart beat are diminished after vagus stimulation which causes a release of acetylcholine Quinidine like procaine and quinine antagonizes the action of acetylcholine in all forms of muscle by raising the threshold for action of acetylcholine If it could be shown that acetylcholine stimulates cardiac muscle in addition to its depressant action then the action of quinidine in the restoration of normal rhythm in auricular fibrillation would be clarified

J H Burn[2] (Oxford Univ) presents evidence that acetylcholine is produced in the auricles by choline acetylase and initiates a contraction when its concentration reaches a threshold value The acetylcholine is then destroyed by cholinesterase and the rate and force of the beat seem to depend on the balance between these two enzymes Excess amounts of acetylcholine—as in vagus stimulation—depress the rate and force of contraction

Auricles of rabbit heart were suspended in oxygenated Locke s solution at 29 C The spontaneous beat stopped after 24 30 hours but addition of acetylcholine in concentrations of 10^{-7} 10^{-6} restored a fairly vigorous beat which continued for some time after removal of the acetylcholine A corollary observation was that the choline acetylase activity of auricles which had spontaneously ceased to beat was much lower than that of freshly excised auricles and auricles which had been restarted by addition of acetylcholine showed a much higher concentration of choline acetylase thereby relating the rhythmic activity of the auricles to the concentration of choline acetylase

(2) La t 1 1161 1164 J 13 1953

geles) filmed by high speed color cinematography the exposed auricles of a patient during mitral commissurotomy and in ECG tracings recorded simultaneously with limb leads auricular flutter at a rate of 240 beats/minute and a 4 1 A V block The camera was operated at 200 frames/second The films projected subsequently at eight frames/second disclosed successive waves of contraction and relaxation engulfing the left appendix from base to apex The right and left appendixes began to contract simultaneously both reached maximal systole at the same instant then began immediately to relax and finally achieved full diastole simultaneously Had a counterclockwise circus movement been present in the fluttering auricles the right appendix would have contracted before the left conversely a clockwise circus movement would have involved the left appendix before the right In slow motion such asynchronism would have been readily apparent The simultaneous activation of both auricular appendixes in this patient was incompatible with the circus movement theory

The spontaneous auricular flutter in this case coincides with the results of experiments with the dog In the common type of flutter the impulse travels from a caudal focus until it reaches the cephalic extremity of the auricles where it terminates Less commonly the impulse arises in the cephalic region travels caudad and terminates at the caudal end This route of propagation of the impulse has been confirmed by multiple esophageal leads recording simultaneously in patients with auricular flutter Further evidence against the circus movement in man is the isoelectric baseline so often occurring after the T_a wave If the mechanism of flutter were a self perpetuating circus movement excitation would presumably be continuous with no isoelectric pause Such an isoelectric pause must indicate auricular diastole and is incompatible with a re entry phenomenon but is readily explained by the theory that flutter originates from a rapidly discharging ectopic focus

Treatment of Paroxysmal Supraventricular Tachycardia with Methoxamine According to Alfred J Berger and Robert L Rackliffe[1] (New Britain Conn) its powerful pressor action in addition to a *vagal effect on the tachycardia make methox*amine very useful in paroxysmal supraventricular tachycardia

(1) J A M A 152 1132 1133 J ly 18 1953

in experimentally implanted fibrin clots is attained in about two hours The concentration within the clot may be sustained at higher levels for longer periods than in plasma Penicillin may continue to act on organisms for some time after the concentration has dropped to subinhibitory levels For these reasons Maxwell Finland[3] (Harvard Med School) advocates frequent intramuscular injections of soluble forms of penicillin rather than use of the longer acting repository preparations A daily dose of 1,200 000 3 000 000 units given in divided doses every two to four hours is adequate If resistance is encountered the dose should be increased rapidly to about 10 000 000 units or more daily Probenecid (0 5 Gm every six hours) may be given to enhance plasma concentrations This compound enhances the blood levels of para aminosalicylic acid but its action may be neutralized by other salicylates It is usually not needed in patients with impaired renal function

Streptomycin is highly useful either alone or with penicillin in daily doses of 2 Gm divided in two or four injections Dihydrostreptomycin is useful if sensitization develops to streptomycin but should generally be saved for that eventuality Bacitracin in doses of 100 000 units daily has only minor and transient effects on renal function and may be useful in conjunction with penicillin in cases of bacterial endocarditis due to gram positive organisms The broad spectrum antibiotics (chlortetracycline oxytetracycline and chloramphenicol) may occasionally be valuable Cures have been reported with these drugs when penicillin and streptomycin have apparently failed Relapses are common however and probably are due to bacteriostatic action of the agents

Patients with negative blood cultures in whom clinical diagnosis is established should be treated with massive doses of penicillin and with treptomycin

Combined Antibiotic Therapy in Subacute Bacterial Endocarditis can be lifesaving when proper combinations of bactericidal drugs are used Bacteriostatic agents (oxytetracycline chlortetracycline chloramphenicol and erythromycin) should not be used regardless of the apparent sensitivity of the organism to one or more of them unless penicillin and streptomycin are proved ineffective These two drugs are

(3) C 1 tio 9 29 99 F bru ry 1954

Choline acetylase activity was determined by preparing an acetone dried powder from the auricles according to an established procedure After suitable incubation the concentration of acetylcholine was evaluated by application of the material to the isolated frog rectus muscle and comparison with solutions of acetylcholine of known concentration When varying amounts of acetylcholine were added to a constant amount of the powdered auricle preceding incubation and compared with the activity of a control of incubated powdered auricle alone it was shown that the addition of acetylcholine depressed the synthesis of acetylcholine by the auricles This validates the observation that when acetylcholine is added to a bath containing contracting auricles the amplitude of the contractions is decreased and the rate slowed

Cholinesterase destroys acetylcholine and eserine inhibits the action of cholinesterase When low concentrations of eserine were added to the organ bath containing contracting auricles the amplitude always increased Increase of the concentration of eserine further increased the amplitude until a concentration of 10^{4} was reached when there was a decrease in the force of contraction It was at this point that the concentration of acetylcholine was in excess of the optimal concentration The heart rate was increased in the lowest concentrations of eserine and decreased in greater concentrations It was demonstrated however that the optimal concentration for the fastest heart rate was not related to the optimal concentration for the greatest force of beat

These observations are considered to be evidence that the rhythmic contractions of the heart are due to the local production of acetylcholine Irregularities of beat may well be due to irregularities of acetylcholine formation

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MISCELLANEOUS DISORDERS OF THE HEART

Treatment of Bacterial Endocarditis Dosage of Penicillin, Use of Other Antibiotics and Treatment of Patients with Negative Blood Cultures The bacterial nidus in endocarditis is relatively well protected from elements within the blood including antibodies leukocytes and antibiotics However equilibrium between concentration of penicillin in plasma and

Anorexia vomiting and failure to gain weight are common and sometimes malaise and irritability are present Physical examination reveals an acutely and seriously ill child with tachypnea and tachycardia disproportionate to temperature elevation Pallor sweating and cyanosis are usually present Frequently there are gallop rhythm and evidence of congestive heart failure and cardiomegaly

From their data and a review of the literature the authors propose the following features to help in differential diagnosis

Glycogen storage disease of the heart (1) age at onset 2 6 months never beyond 18 months (2) history of a similar disorder in a sibling (3) absence of congestive failure in the presence of marked cardiomegaly and (4) skeletal muscle biopsy showing high glycogen content

Aberrant left coronary artery (1) onset at age 2 6 months (2) tachycardia respiratory distress cyanosis and attacks of hyperhidrosis (3) absence of congestive failure and (4) x ray evidence of a bulging prominence in the region of the left ventricle

Medial necrosis of the coronary arteries (1) age at onset less than 3 months (2) evidence of systemic disease especially involving the kidneys (3) associated congenital anomalies and (4) absence of congestive failure

Idiopathic (Fiedler s) myocarditis and subendocardial sclerosis are both characterized by (1) age at onset after 6 months (2) presence of abnormal heart sounds (3) evidence of congestive heart failure and (4) good response of the congestive failure to digitalis therapy Clinically these two diseases are indistinguishable

Fourteen Cases of Idiopathic Myocarditis in Infants and Children are reported by Howard Williams R N O Reilly and Alan Williams[6] (Melbourne) They are classified in two types (1) acute with sudden onset high mortality and little cardiac damage in survivors (2) subacute and chronic with insidious onset lower mortality and higher incidence of cardiac abnormalities in those surviving

After a few days of malaise slight fever and nonspecific complaints the children with acute myocarditis rapidly became seriously ill with circulatory and respiratory embarrassment pallor and cyanosis Temperature was subnormal

(6) A ch D Ch ldhood 28 271 83 A gu t 1953

synergistic and are particularly effective in enterococcic infections Lowell A Rantz[4] reports that only a small proportion of cases caused by bacteria other than streptococci will not be cured by streptomycin and penicillin A satisfactory regimen for use with penicillin sensitive strains consists of 1 000 000 units of procaine penicillin twice daily and 1 Gm of equal parts of streptomycin and dihydrostreptomycin Cure is often effected in two weeks If enterococci and other penicillin resistant streptococci are involved the patient should be treated for a month or more with larger amounts of penicillin Probenecid may be added After treatment all patients should rest six to eight weeks regardless of duration of therapy to permit solid healing of valves and resolution of myocarditis which apparently is responsible for heart failure in many instances

Three errors are commonly made in treatment of subacute bacterial endocarditis Often the disease is not recognized early enough The possible significance of fever in patients with heart murmurs should be constantly kept in mind particularly when associated with anemia renal lesions or cerebrovascular disturbances Another error lies in the use of bacteriostatic drugs It is believed that the organisms implanted on the heart valves are invulnerable to the usual cellular and immune clearing mechanisms and must be killed in situ The third mistake is indecisiveness and poor planning Needless changes in therapy should not be made

Primary Myocardial Disease in Infancy and Childhood is characterized by (1) cardiomegaly (2) absence of significant murmurs (3) ECG abnormalities and (4) normal blood pressure It is separate from rheumatic heart disease and common congenital heart anomalies Harold D Rosenbaum Alexander S Nadas and Edward B D Neuhauser[5] (Harvard Med School) discuss 45 patients with this clinical picture Autopsy on 26 disclosed that 10 had idiopathic myocarditis 10 subendocardial sclerosis 3 glycogen storage disease of the heart 2 medial necrosis of the coronary arteries and 1 an aberrant left coronary artery These five pathologic entities produce a *clinical syndrome characterized by rapid onset* respiratory distress with intermittent cyanosis and occasionally a cough

(4) Stanford M Bull 12 263 February 1954
(5) A M A Am J Dis Child 86 844 July 1953

Only one patient had no ECG changes but on auscultation a splashing sound due to simultaneous presence of air and fluid in the pericardial sac was heard At follow up 45 90 months after the accident only one of the nine patients traced had serious signs of heart disease This patient complained of precordial pain palpitation dyspnea and faintness on exertion There were slight tenderness over the precordium changes in the ventricular complexes and T waves with exercise and extrasystoles were present Two more patients had slightly enlarged hearts In one however enlargement may have resulted from rheumatic fever Most of the nine patients had nervous complaints interpreted as symptoms of traumatic cardiac neurosis

Traumatic heart disease probably would be recognized more often if all patients with chest injuries had repeated auscultation and ECGs during the weeks following trauma Treatment should be bed rest until symptoms subside and ECG is constant usually about six weeks

[Contusion of the heart is a rather common condition and frequently results from automobile accidents with impact of the chest on the steering wheel of the car The resulting ECG changes may be permanent and may lead to an erroneous diagnosis of coronary disease years later —Ed]

Aneurysm of Heart Correlative Study of 102 Proved Cases Although gummatous rheumatic and mycotic processes can produce ventricular aneurysms the commonest cause is through and through myocardial infarction J Schlichter H K Hellerstein and L N Katz[8] (Michael Reese Hosp) analyzed 108 ventricular aneurysms (102 patients) due to this cause and proved at autopsy All were located in large infarcts and showed distinct bulges or sacculations with marked thinning of the ventricular wall Acute aneurysms were observed as early as two days after infarction and chronic aneurysms located in old infarcts could be seen one month after coronary occlusion In no case did a ventricular aneurysm rupture although there was one instance of rupture of a septal aneurysm

Radiologic demonstration of paradoxical pulsation in a localized bulge of the heart of a patient with a large myocardial infarction is the most conclusive diagnostic evidence The ECG features are a residual pattern of myocardial infarction persistent S T deviations and the small R_1 deep S_2 and S_3 pattern

(8) M d 33 43 86 F bru ry 1954

normal or slightly elevated Pulmonary emphysema was frequent and respiratory rate increased to 100/minute Heart sounds were usually of poor quality and in some gallop rhythm indicated cardiac embarrassment The liver edge was palpable 3 or 4 fingerbreadths below the costal margin X ray of the chest showed gross uniform cardiac enlargement The ECG abnormalities were typically low voltage QRS complexes especially in lead I and low isoelectric or inverted T waves in the standard leads Two of nine patients survived At autopsy all hearts were dilated and most showed hypertrophy The myocardium was flabby and microscopically there was widespread but often patchy damage to the myocardium with associated inflammatory reaction With one exception the pericardium endocardium and valves were normal Death usually occurred within 24 hours

Patients with subacute myocarditis had symptoms of vague ill health for a month or more before myocardial failure developed The clinical picture x ray findings and ECG apparently were similar to those in the acute type but the children were not gravely ill All responded to digitalis therapy Four of five patients survived but all had residual cardiac damage and two had a mitral lesion

This condition may be of infectious origin The acute form is commonly mistaken for pneumonia as respiratory embarrassment and cyanosis are the outstanding clinical features and cardiac enlargement is difficult to detect clinically Management includes digitalis and oxygen therapy

Traumatic Heart Lesions are probably considerably more common and carry a less serious prognosis than is generally believed Robert Enig and Erik Rud[7] (Herning Denmark) report on 11 patients with traumatic heart lesions 5 were buried in an avalanche of sand and 6 were struck in the chest Only four had fractured ribs Some were rendered unconscious and some were cyanotic following injury The commonest ECG changes were variations in height of the T waves (seven) and transitory auricular fibrillation or flutter (five) Not all ECG changes were beyond normal limits but were interpreted as pathologic because they represented variations in each patient s usual ECG Duration of bed rest was decided mainly on the basis of continuance of variations in the ECG

(7) Acta m d sca d n 146 393 410 1953

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(8) Med 33 43-86 F bru ry 1954

Mural thrombosis and thromboembolic phenomena oc curred more than twice as often in the group with ventricular aneurysms as in a control group of 410 patients with infarction but no aneurysms Hypertension was significantly more fre quent in the group with aneurysms and the incidence of valvu lar deformities of dynamic significance or malformation of the great vessels which also tend to increase the load on the heart was unusually high

Bed rest for four to six weeks or more after myocardial infarction is considered adequate On this basis two thirds of the patients with aneurysm had had either no or inadequate bed rest Thus increased heart work seems to facilitate aneu rysm formation

Prognosis for patients with ventricular aneurysm is poor 73% of the present series died within three years after infarc tion The terminal stage was dominated by congestive heart failure in 70% and was the main cause of death in 48 1% In 21 7% the main cause of death was thromboembolic phe nomena

Tic of Respiratory Muscles Report of Three Cases and Review of Literature is presented by William Dressler and Morris Kleinfeld[9] (State Univ of New York Brooklyn) Ob servations on 2 patients with diaphragmatic flutter fibrillation and one with intercostal muscular tic are collated with those on 17 others previously reported The rate of spastic move ments ranged from 60 to 300/minute and the rhythm was generally irregular The diaphragmatic excursion as viewed by fluoroscope ranged from 5 to 10 mm but in one instance measured 6 in Tic of the intercostal muscles may simulate aortic aneurysm or cardiomegaly by the amplitude of its pul sations Clinically pain has not generally been a significant symptom exhaustion was the chief complaint of a large num ber of the patients who had protracted attacks of diaphrag matic spasm Vibratory movements of the chest and abdominal wall were the most significant finding

Central stimulation of the phrenic nerve often a cause of this disease may result from epidemic encephalitis Irritation of the phrenic nerve along its course—as by scar tissue cer vical rib neoplasm abscess or by the contracting heart itself—may produce the clinical picture Peripheral disturbances act

(9) Am J Med 16 61 72 J y 1954

ing along the termination of the phrenic nerve or on the muscle itself include hemorrhage into the diaphragm abdominal adhesions fractured xiphoid process intestinal obstruction peritonitis or diaphragmatic pleurisy Two of the authors three patients with diaphragmatic flutter had mitral stenosis and pronounced cardiac enlargement the significance of this factor in the genesis of respiratory tic is undetermined

Prompt relief of the diaphragmatic tic will as a rule result from procaine block or freezing of the phrenic nerves although it is likely to recur Section or crushing of the phrenic nerves has also produced only temporary relief exacerbation occurred on regeneration of the severed nerve fibers Spasm of the diaphragm can be relieved permanently only by total avulsion of the phrenic nerves The inactivity of the diaphragm that results is usually remarkably well tolerated

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PULMONARY CIRCULATION

Recent Studies in Primary Pulmonary Hypertension Including Pharmacodynamic Observations on Pulmonary Vascular Resistance are discussed by David T Dresdale Robert J Michtom and Martin Schultz[1] Primary pulmonary hypertension is distinguished from the secondary form by absence of (1) intrinsic heart or lung disease and (2) mechanical blocks in the pulmonary vascular bed seeded from without e g pulmonary emboli It is associated with right ventricular hypertrophy and may or may not be accompanied by pulmonary vascular changes These vascular changes are predominantly atheromatous lesions of the stem and large elastic arteries alone or in conjunction with fibrous intimal thickening and narrowing or obliteration of the smaller arteries

Clinical features are exertional dyspnea and weakness exertional substernal and left chest pain resembling angina exertional syncope palpitation orthopnea (usually terminally only) and hemoptysis (rare) Venous pressure is elevated and the heart shows evidence of right ventricular hypertrophy The second pulmonary sound is accentuated and pulmonary systolic and diastolic murmurs may be heard Cyanosis without clubbing of the fingers may be seen Results of pulmonary

(1) B Il N w Y k Ac I M 1 30 195 207 M h 1954

Mural thrombosis and thromboembolic phenomena occurred more than twice as often in the group with ventricular aneurysms as in a control group of 410 patients with infarction but no aneurysms Hypertension was significantly more frequent in the group with aneurysms and the incidence of valvular deformities of dynamic significance or malformation of the great vessels which also tend to increase the load on the heart was unusually high

Bed rest for four to six weeks or more after myocardial infarction is considered adequate On this basis two thirds of the patients with aneurysm had had either no or inadequate bed rest Thus increased heart work seems to facilitate aneurysm formation

Prognosis for patients with ventricular aneurysm is poor 73% of the present series died within three years after infarction The terminal stage was dominated by congestive heart failure in 70% and was the main cause of death in 48 1% In 21 7% the main cause of death was thromboembolic phenomena

Tic of Respiratory Muscles Report of Three Cases and Review of Literature is presented by William Dressler and Morris Kleinfeld[9] (State Univ of New York Brooklyn) Observations on 2 patients with diaphragmatic flutter fibrillation and one with intercostal muscular tic are collated with those on 17 others previously reported The rate of spastic movements ranged from 60 to 300/minute and the rhythm was generally irregular The diaphragmatic excursion as viewed by fluoroscope ranged from 5 to 10 mm but in one instance measured 6 in Tic of the intercostal muscles may simulate aortic aneurysm or cardiomegaly by the amplitude of its pulsations Clinically pain has not generally been a significant symptom exhaustion was the chief complaint of a large number of the patients who had protracted attacks of diaphragmatic spasm Vibratory movements of the chest and abdominal wall were the most significant finding

Central stimulation of the phrenic nerve often a cause of this disease may result from epidemic encephalitis Irritation of the phrenic nerve along its course—as by scar tissue cervical rib neoplasm abscess or by the contracting heart itself—may produce the clinical picture Peripheral disturbances act

(9) Am J M d 16 61 2 J y 1954

ing along the termination of the phrenic nerve or on the muscle itself include hemorrhage into the diaphragm abdominal adhesions fractured xiphoid process intestinal obstruction peritonitis or diaphragmatic pleurisy Two of the authors three patients with diaphragmatic flutter had mitral stenosis and pronounced cardiac enlargement the significance of this factor in the genesis of respiratory tic is undetermined

Prompt relief of the diaphragmatic tic will as a rule result from procaine block or freezing of the phrenic nerves although it is likely to recur Section or crushing of the phrenic nerves has also produced only temporary relief exacerbation occurred on regeneration of the severed nerve fibers Spasm of the diaphragm can be relieved permanently only by total avulsion of the phrenic nerves The inactivity of the diaphragm that results is usually remarkably well tolerated

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PULMONARY CIRCULATION

Recent Studies in Primary Pulmonary Hypertension Including Pharmacodynamic Observations on Pulmonary Vascular Resistance are discussed by David T Dresdale Robert J Michtom and Martin Schultz[1] Primary pulmonary hypertension is distinguished from the secondary form by absence of (1) intrinsic heart or lung disease and (2) mechanical blocks in the pulmonary vascular bed seeded from without e g pulmonary emboli It is associated with right ventricular hypertrophy and may or may not be accompanied by pulmonary vascular changes These vascular changes are predominantly atheromatous lesions of the stem and large elastic arteries alone or in conjunction with fibrous intimal thickening and narrowing or obliteration of the smaller arteries

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(1) B ll N w Y k A d M d 30 195 207 M b 1954

function studies are within normal limits Catheterization of the right heart shows elevated pulmonary artery pressure with normal systemic artery pressure low cardiac output increased A V oxygen difference with normal arterial oxygen saturation and elevated right ventricular end diastolic pressure X ray study reveals right ventricular hypertrophy bulging pulmonary artery segment prominent hilar vessels and normal or decreased intrapulmonary vascular markings The disease runs a malignant course characterized by right heart failure often terminating in sudden death

Priscoline® causes a striking fall in pulmonary artery pressure with increase in blood flow and symptomatic improvement affecting pulmonary vascular resistance more than systemic resistance This is further evidence that pulmonary hypertension depends partially on increased vascular tone which is probably present in the precapillary bed Pulmonary capillary pressure greater than 30 mm Hg causes pulmonary edema

Priscoline® given to patient with severe pulmonary emphysema caused a drop in pulmonary vascular resistance and a fall in arterial oxygen saturation from 96 to 87% suggesting that poorly ventilated areas in the lungs were perfused after priscoline® administration

Etiology of Secondary Pulmonary Hypertension M Irene Ferrer and Rejane M Harvey (Columbia Univ) discuss the following causes of this disease (1) increased pulmonary blood flow (2) left ventricular failure (3) anoxia (4) alteration of the pulmonary vascular bed by emboli sclerosis or fibrosis and (5) mitral stenosis

Increased pulmonary blood flow in congenital heart disease may antedate pulmonary hypertension with right ventricular hypertrophy developing as the heart pumps an increased load The succeeding increased pulmonary vascularity may itself precede vascular sclerosis This explains why surgical correction of the cause of increased pulmonary flow may be followed in some cases by return to normal pressures

In left ventricular failure there often will be pulmonary artery hypertension and a normal filling pressure in the right ventricle thus confirming the thesis of isolated ventricular failure Right ventricular filling pressure and systemic venous

( ) Bull N w Y k Ac d M d 30 208 220 March 1954

pressure subsequently rise as that side of the heart fails Digitalization is restorative particularly when failure has not been of long duration

The cause of the pulmonary hypertension determines the prognosis in chronic cor pulmonale Anoxia produced by emphysema can often be successfully treated On the other hand when anoxia is due to fibrosis (including silicosis sarcoidosis beryllios1s and scleroderma) or to multiple pulmonary emboli irreversible anatomic alterations produce irreversibility of the elevated vascular resistance and reduction of activity to a minimum (and hence reduction of pulmonary artery pressure) is the only therapy

Mitral stenosis may cause pulmonary hypertension in three differing ways mechanical block of the stenotic valve pulmonary vascular sclerotic lesions and left ventricular failure Digitalis will relieve the component of myocardial insufficiency and cardiac surgery will reduce the valvular block Pulmonary vascular sclerosis is not amenable to correction although it may recede with time following relief of other causes of hypertension

Treatment of Chronic Cor Pulmonale begins with a correct diagnosis of the lung disease causing it the commonest of which include chronic obstructive emphysema different types of pulmonary fibrosis and granulomatous lesions which may eventually result in fibrosis The presence of emphysema does not automatically imply the coexistence of fibrosis Rejane M Harvey M Irene Ferrer and Andre Cournand[3] (Columbia Univ) discuss the diagnosis and management of the more common types of chronic cor pulmonale emphasizing the necessity of an attack on the pulmonary lesion causing the heart failure

There are three fundamental disturbances in pulmonary function in chronic pulmonary emphysema (1) gross impedance to air flow in and out of the lungs (2) uneven distribution of air to the alveoli and (3) similar uneven distribution to the alveoli of blood returning to the lungs Although the third derangement cannot be attacked therapeutically the first two can be remedied Since the inadequate air flow is caused by loss of elasticity bronchiolar spasm and mucosal edema and obstruction from secretions and exudates vapor

(3) C cul t 7 932 940 J 1953

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(2) B ll New Yo k A d Med 30 208 220 M ch 1954

with diffuse fibrotic disease which encroaches on the pulmonary vasculature restricting expansion In silicosis pulmonary dysfunction may remain one of ventilatory insufficiency without arterial anoxia or right heart failure These patients tend to have a low output heart failure if it occurs In the alveolar capillary block syndrome which includes various granulomas of the lung (beryllium Boeck s sarcoid and those of undetermined origin) scleroderma and the diffuse reticular pulmonary fibroses the cardiac output is elevated and there is mild (often progressive) pulmonary hypertension increasing with exertion Treatment for these pulmonary fibrotic diseases is along the same principles as for emphysema but the results are not so good Physical activity should be rigorously restricted

If obstructive emphysema and fibrosis coexist as they may treatment should be directed toward relief of the manifestations of emphysema

Relief of Pulmonary Hypertensive Pain after Mitral Commissurotomy is reported by Edward J Mears W Proctor Harvey and Charles A Hufnagel[4] (Georgetown Univ)

Woman 50 had severe precordial pain brought on by exertion A diagnosis of coronary artery disease had been made The pain did not respond to nitroglycerin but narcotics gave some relief She was thought to have mitral stenosis on the basis of history and physical findings but was considered a poor surgical risk because of what was at first thought to be angina pectoris An ECG showed incomplete right bundle branch block with what was reported as changes consistent with myocardial ischemia Four months later a re evaluation of symptoms as manifestations of pulmonary hypertensive pain led to mitral commissurotomy at which time a tight mitral stenosis and a greatly dilated pulmonary artery were found There was immediate and dramatic relief from the precordial pain which did not recur for several months At that time she began to have exacerbations of congestive heart failure and it was noted that with accumulation of about 10 lb edema fluid the pulmonary hypertensive pain reappeared whereas during periods of cardiac compensation she was free from pain When pain did recur with congestive failure it rapidly responded to diuretics and the usual medical care

Although coronary artery disease could not be absolutely excluded in this case the disappearance of pain after commissurotomy suggests that pulmonary hypertension was the major if not the sole cause

(4) N w E gl nd J M d 49 71 718 Oct 29 1953

ized bronchodilators are very beneficial especially if used with a positive pressure apparatus to increase dissemination Intensive use of antibiotics to eliminate even minor pulmonary infections is important

Grave complications—pulmonary hypertension hypervolemia polycythemia and right heart failure—occur when anoxia and hypercapnia become dominant features of emphysema If anoxia exists without hypercapnia oxygen should be applied However in the hypoventilating patient with carbon dioxide retention in addition to the anoxia the respiratory response to carbon dioxide is diminished and oxygen want operating through the carotid body receptors remains the primary stimulus to breathing *Oxygen therapy* may further reduce alveolar ventilation by destroying the respiratory stimulus thus causing a further rise in carbon dioxide tension with narcosis and death In all emphysematous patients one should determine the carbon dioxide content of the arterial blood before oxygen therapy is started If hypercapnia is present some mechanical means should be used to maintain adequate alveolar ventilation while oxygen is being supplied

Treatment of the heart failure is the same as that for heart disease of other etiology Arrhythmias are rare Should hydrothorax exist the improvement in lung function from thoracentesis should be carefully weighed against the real danger of inducing a *pneumothorax by the procedure Blood flow* and blood volume in secondary polycythemia must be reduced by phlebotomies 300 500 cc being removed each time Diagnosis of this secondary polycythemia rests on a high hematocrit reading with hypochromic red cells Sufficient blood should be removed to reduce the hemoglobin level below 12 Gm and the hematocrit reading to 45 50% Phlebotomies should be done no more often than every two or three days Adjunctive therapy with steam inhalation sputum liquefiers adequate fluid and caloric intake and good nursing care is essential In the maintenance therapy of these patients the importance of bed rest cannot be overemphasized since the arterial blood oxygen saturation *already low at rest becomes much lower* on exertion and may even fall to 45% in this type of emphysematous patient Abdominal belts breathing exercises pneumoperitoneum and mechanical respirators may be helpful

Chronic cor pulmonale due to pulmonary fibrosis occurs

its origin and at its first bifurcation the vertebral arteries at the atlas the lower extremity and the bifurcation of the basilar artery the posterior cerebral artery as it winds posteriorly around the cerebral peduncle and the anterior cerebral artery as it curves upward around the genu of the corpus callosum In normotensive persons atherosclerosis tends to spare the surface branches of the cerebrum and cerebellum and the penetrating branches to the lenticular nucleus and internal capsule arising from the stem of the middle cerebral artery and to the thalamus and brain stem from the basilar system In hypertension however these groups are particularly likely to be affected and a more uniform layer of deposit tends to form in the larger arteries

Symptoms of cerebral atherosclerosis result from occlusion following bulging of an intimal plaque into the lumen or more commonly superimposed thrombosis Atherosclerosis probably plays no important part in primary intracerebral hemorrhage Symptoms may follow the intracerebral lodgement of atheromatous emboli that break off from the aorta Atherosclerosis does not in itself cause symptoms unless hypotensive vascular collapse occurs when ischemia distal to a partially occluding plaque may be present In most cases symptoms are elicited only when actual thrombosis is superimposed

Senile dementia is too often attributed to arteriosclerosis Dementia and other syndromes such as parkinsonism and epilepsy can be laid to cerebral atherosclerosis only if they result from thrombosis which is generally sudden

Influence of Age, Anesthesia and Cerebral Arteriosclerosis on Cerebral Vascular Activity to CO_2 was studied in 55 patients by James F Schieve and William P Wilson[6] (Duke Univ) who attempted to find a means of quantitatively predicting the degree of cerebral vascular sclerosis Previous studies have shown that there may be a low cerebral blood flow (CBF) in the absence of structural changes in blood vessels If full vasodilatation of the vessels of the brain could be produced it was thought that by measuring the consequent CBF it might be possible to separate patients with decreased blood flow due to structural changes in the vessels from those with decreased blood flow due to other causes

(6) Am J M d 15 171 174 A gu t 1953

Although the pain of pulmonary hypertension may mimic angina pectoris closely there are a few important differences *It is frequently associated with dyspnea and often accentuated* by respiration The duration varies from several minutes to months thus imitating the duration of all phases of coronary insufficiency or myocardial infarction The ECG (as in this case) may show T wave changes or RS T deviations or both Nitroglycerin may afford partial or equivocal relief from the pain of pulmonary hypertension but usually it is ineffective Some patients have a varying degree of cyanosis and cough is common The presence of a condition associated with increased pressure in the pulmonary circuit as congenital heart disease primary diffuse disorders of the lung and disorders of the pulmonary artery is essential to production of this pain

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CEREBRAL CIRCULATION

Concerning Cerebral Arteriosclerosis To clarify many misconceptions and to correct the tendency to attribute many symptoms incorrectly to this condition Miller Fisher[5] (McGill Univ) examined some 1 500 brains at autopsy He used for his study the following classification (1) degenerative arteriopathies—atherosclerosis medial arteriosclerosis arterionecrosis (2) *productive or hyperplastic arteriopathies* or both—medial and/or intimal changes often associated with hypertension (3) inflammatory arteriopathies—arteritis due to infection allergy chemical or physical agent or trauma—and thromboangiitis obliterans and (4) combined forms of arteriopathies Atherosclerosis is the only arterial disease of major importance in the production of cerebral symptoms and lesions

The degree of atherosclerosis of the cerebral arteries roughly parallels its severity elsewhere in the body It is not mirrored by the radial artery which has long been known to escape the changes that occur in other vessels or in the retinal vessels because atherosclerosis is not found in vessels of such small caliber Special sites of predilection are the carotid sinus the paraclinoid portion of the internal carotid near the origin of the ophthalmic artery the middle cerebral artery at

(5) J Am Geriat Soc 1 18 J ary 1954

its origin and at its first bifurcation the vertebral arteries at the atlas the lower extremity and the bifurcation of the basilar artery the posterior cerebral artery as it winds posteriorly around the cerebral peduncle and the anterior cerebral artery as it curves upward around the genu of the corpus callosum In normotensive persons atherosclerosis tends to spare the surface branches of the cerebrum and cerebellum and the penetrating branches to the lenticular nucleus and internal capsule arising from the stem of the middle cerebral artery and to the thalamus and brain stem from the basilar system In hypertension however these groups are particularly likely to be affected and a more uniform layer of deposit tends to form in the larger arteries

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(6) Am J M d 15 171 1 4 A gu t 1953

METHOD—Cerebral blood flow was determined by the Kety Schmidt nitrous oxide technic with the Scheinberg Stead modification Oxygen differences (A VO) were determined by the Hickam Frayser method and were made on the integrated arterial and cerebral venous blood specimens Cerebral oxygen consumption ($CMRO_2$) was calculated by multiplying the respective CBF and A VO. After the control CBF determination was made, the patient breathed 5 or 7% CO. for four minutes It has been previously *shown that this CO concentration does not significantly change* the CMRO By assuming that this value was constant the CBF following CO_2 inhalation could be calculated Eight patients were anesthetized with 0 6 1 5 Gm thiopental sodium given intravenously over 10 30 minutes

A slight decrease in vascular reactivity was found in 29 normal subjects which could be correlated with age Ten patients who had had strokes showed reduction in CBF $CMRO_2$ and response to CO_2 No significant difference was found in CBF or $CMRO_2$ of eight patients with organic brain disease as compared with those who had had strokes but they showed essentially the same reactivity to CO as the older normal subjects

Eight patients with no demonstrable vascular disease were *anesthetized with thiopental It was found that when the* $CMRO_2$ was greatly depressed by anesthesia a significant decrease in responsiveness to CO. followed It could not be determined whether this was due to depression of cerebral metabolism or to the direct depressant action of thiopental on cerebral vessels

This technic appears to have practical application in separating patients with dementia due to severe cerebral *arterio*sclerosis from patients with dementia due to primary parenchymal brain degeneration

Cerebral Vascular Insufficiency Explanation of Some Types of Localized Cerebral Encephalopathy The blood flow to each cerebral hemisphere is essentially autonomous for the collateralization furnished by the circle of Willis does not function when blood pressure in both sides of the brain is equal Blood from the right and left vertebral arteries does not normally intermingle in the basilar artery When the blood flow to one side of the brain is compromised the collateral circulation furnished in these two systems may not be adequate

Eliot Corday Sanford F Rothenberg and Tracy J Putnam[7] (Univ of California Los Angeles) propose a concept—cerebral vascular insufficiency—the pathogenesis of which becomes manifest if it is assumed that cerebral blood flow basically adheres to two physical principles (1) the velocity of flow in a tube of given caliber is proportionate to the pressure of the fluid and (2) the pressure remaining constant the volume of flow per unit time is proportionate to the fourth power of the diameter of the tube (Poiseuille s law) If the caliber of an artery is reduced by arteriosclerosis to half its normal value the volume flow through this artery would be reduced to 1/16 its previous level provided the pressure remained constant Should pressure then be reduced reduction in volume flow would be still greater Thus localized narrowing of the arterial tree in combination with hypotension can readily lead to severe ischemia of the area supplied by the involved vessel If hypotension is severe the collateral circulation will al o fail further endangering the already ischemic region

Latent insufficiency of oxygenation of the brain on the basis of arteriosclerosis may be made apparent by periods of shock This concept analogous to acute coronary insufficiency has experimental and clinical support and may explain the mechanism of certain clinical observations

If hypotension is induced and maintained in monkeys whose middle cerebral arteries have been surgically occluded abnormal encephalographic patterns appear which had not been present during periods of normotension and which disappear if the normal level of systemic blood pressure is restored *fairly promptly Such experiments have their clinical* counterparts in many heterologous circumstances all of which however share the factor of systemic hypotension

A case is cited in which hemianesthesia and hemiplegia with rather severe hypotension developed in a hypertensive patient who vomited large amounts of blood Restoration of normal blood pressure was followed by complete regression of neurologic signs Here cerebral vascular insufficiency had developed concurrent with hypotension which itself had developed secondary to gastric hemorrhage

Other factors which cause shock may produce neurologic

(7) A M A A b Neu l & P y h t 69 551 570 M y 1953

sequelae which can often be reversed by correction of the hypotension The importance of elevating the blood pressure is apparent for many such manifestations quickly disappear

Aortic Arch Syndromes Diminished or Absent Pulses in Arteries Arising from Arch of Aorta Richard S Ross and Victor A McKusick[8] (Johns Hopkins Univ) discuss cases in which the seat of the disorder is near the origin of the great vessels from the arch of the aorta Causes of this syndrome are numerous but syphilis is by far the most common Presence of an aneurysm is by no means essential and syphilitic aortitis with or without dilatation can produce the syndrome by intimal proliferation and cicatrization Atheromatosis is seldom a primary cause but often is a further insult in other causes such as syphilis Trauma may play a role in development of the aortic arch syndrome often there can be serious vascular injury with little external manifestation Congenital and hereditary anomalies are perhaps not so significant as thought However many patients with this condition have uncommon branching patterns of the great vessels at the aortic arch Thrombocytosis may be a contributing factor in lack of pulsations in the great vessels arising in the arch Healed dissecting aneurysms of the aorta can undoubtedly account for pulse differences In many cases obstruction of the large branches of the aortic arch at their origin is part of a generalized nonsyphilitic arteritis Pulse change due to extravascular upper mediastinal tumor is uncommon The aortic arch syndrome must be differentiated from neurogenic pulse changes peripheral embolism and the syndrome of the thoracic outlet or hyperabduction syndrome

Symptoms of ischemia in the arm are minimal but many disorders result from carotid embarrassment These include dizziness vertigo headache and visual symptoms which are manifest as blindness or scotomas occurring with exertion—visual claudication Necrosis of the nasal septum and perforation may result from chronic ischemia or infarction Carotid sinus hypersensitivity is frequent Treatment is aimed at the underlying disease if possible

Management of Cerebral Vascular Accidents including cerebral thrombosis embolism and hemorrhage subarachnoid hemorrhage unruptured or leaking congenital aneurysm of

(8) A M A A ch Int M d 92 701 740 N embe 1953

the cerebral vessels and subdural hematoma is outlined by J M Nielson[9] (Los Angeles)

Cerebral thrombosis is preceded by a general lowering of circulatory efficiency manifested by paresthesias or mild weakness or visual disturbances If the patient can be reached within a few hours of onset either a procaine block of the contralateral stellate ganglion should be done or 500 mg procaine in 500 cc of normal saline should be given intravenously over a two hour period There seems little doubt that vasospasm occurs in cerebral vessels

Embolism occurs so suddenly that if the vessel is of any material size the patient drops as though shot The source of embolism is usually disclosed by auricular fibrillation cardiac murmur or some other indication Procaine intravenously is good treatment for the immediate problem but the chief consideration in long term management is the source of the embolus

Most cerebral hemorrhages result from vasomotor paralysis and diapedesis of the red cells rather than a blow out of a large vessel A small localized hemorrhage may be surgically drained thereby obviating a foreign body reaction that might cause epilepsy In the comatose patient with massive cerebral hemorrhage the cerebrospinal fluid is grossly bloody He should be put to bed with head elevated and an ice cap to induce vasoconstriction little else can be done

Persistent and recurrent migraine syndromes that remain relatively fixed anatomically suggest an aneurysm in the circle of Willis Diagnosis is established by angiography Rupture or leakage of an aneurysm generally causes severe localized headache vomiting stupor or loss of consciousness then nuchal rigidity and most likely extraocular palsy with diplopia The cerebrospinal fluid is always bloody and usually under increased pressure The picture is that of meningitis Deep coma without nuchal rigidity or Kernig s sign may also occur

With subdural hematoma the pupil on the side of the hemorrhage whether larger or smaller than the other will react poorly if at all to light Hemiplegia arising from subdural hematoma differs from that caused by cerebral hemorrhage or thrombosis in that it is spastic throughout its course

(9) A I I M d 39 717 72 O 1953

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Management of Cerebral Vascular Accidents, including cerebral thrombosis embolism and hemorrhage subarachnoid hemorrhage unruptured or leaking congenital aneurysm of

(8) A M A A ch I t Med 92 701 740 No mb 1953

Studies of Vasospasm. I. Use of Glyceryl Trinitrate as Diagnostic Test of Peripheral Pulses. Absence of peripheral pulses may be due to vasospasm, organic arterial occlusion or congenital abnormality. It may also be due to shock or exsanguinating hemorrhage. Accurate diagnosis of the cause of impalpable peripheral pulses is facilitated by a rapid method to relieve the vessels of spastic phenomena which may be caused by emotional stimuli, cold or trauma in normal arteries or may be a manifestation of vasospastic disease, as with Raynaud's phenomenon.

William T. Foley, Ellen McDevitt, J. A. Tulloch, Martin Tunis and Irving S. Wright[2] (New York Hosp.-Cornell Med. Center) found that sublingual administration of 0.4 mg. glyceryl trinitrate, by producing relaxation of smooth muscle throughout the body, increased amplitude of palpable pulsations of arteries which were not organically occluded. They tested 19 normal subjects, 29 patients with increased vasomotor tone and 48 with occlusive arterial disease. A definite increase in pulsation was noted in 18 normal subjects following use of the drug and a slight increase in 1. All patients with vasospastic disease had increase in oscillometric readings and peripheral pulses became bounding in character. As with the normal subjects, color and temperature of hands and feet did not change except in six patients, whose extremities became pinker and warmer. In the patients with occlusive vascular disease there was occasionally a small increase in oscillometric readings which was interpreted as possibly indicating an effect on collateral channels. Pulses distal to complete obstruction did not become palpable, however.

No complications were encountered other than mild flushing of the head and slight headache. Use of glyceryl trinitrate is contraindicated in cases of recent myocardial infarction, anemia, increased intraocular or intracranial pressure. It should not be used when maintenance of vasomotor tone is important, as in shock, febrile conditions and debilitation.

(2) C[illegible] 7:847-854, J[illegible] 1953.

X ray of the head may disclose displacement of the pineal body The cerebrospinal fluid may be pink because of arachnoid injury Other diagnostic criteria though helpful may also be misleading

Treatment of Incipient Apoplexy with Intravenous Aminophylline is outlined by Fr Mainzer[1] (Anglo Swiss Hosp Alexandria Egypt) who considers it clinically established that vasospasm is significant in a large portion of patients with cerebral thrombosis A pertinent observation is the evanescent and sometimes permanent blindness consequent to ophthalmic migraine in which the mechanism is vasospasm Since this condition occurs in the retinal arteries it is logical that it may obtain in cerebral arteries as well

Clinical and experimental data concerning cerebral circulation are inconsistent Kety demonstrated a diminution of the total cerebral blood flow after administration of aminophylline The author considers that an important mechanism of the dramatic effect of aminophylline in incipient apoplexy is focal vasodilatation an abolition of the initial arterial vasoconstriction at a moment when the nerve tissue has not been irreversibly damaged Another factor in the therapeutic effect of aminophylline is an increase in permeability of the blood brain barrier, by which theophylline may enhance removal of toxic metabolites accumulated during the preceding ischemic period and the regression of focal edema a washing out function of the blood There is rapid and considerable decrease in intrathecal pressure after intravenous administration of aminophylline which is interpreted as diminution in the water salt content of the central nervous system

Mainzer reports seven cases in which aminophylline (usually 0 24 Gm) given intravenously within 45 minutes after onset of symptoms abolished all manifestations of apoplexy including coma in five instances and hemiplegia in two In two other cases the treatment failed One patient was relieved of symptoms due to the angiospasm associated with hypertension

The reported effect of aminophylline in incipient apoplexy is by itself a new and decisive argument for the vasoconstriction concept of cerebrovascular accident

(1) Acta m d scand av 146 362 374 1953

nia) report observations on 12 patients with segmental arterio sclerotic narrowing as the sole cause for symptoms of ische mia 6 with asymptomatic arterial stenosis diagnosed as an incidental arteriographic finding 6 whose original stenotic lesion progressed to complete thrombosis and 3 found to have a significant stenotic lesion apart from a separate zone of arterial thrombosis In all the pathologic changes involved a portion of the major arterial tree between the upper abdominal aorta and the level of bifurcation of the popliteal arteries Aortography was done transcutaneously with injection into the aorta proximal to the celiac axis

The diseased intima was resected in 12 patients The patho logic and arteriographic characteristics of the lesions were closely related The most pronounced degree of stenosis was usually observed near the orifice of a major arterial branch In a zone of stenosis variable portions of the circumference of the artery were thickened some being annular napkin ring lesions and others eccentric thickenings of one wall pro jecting into the lumen sufficiently to create a crescent shaped lumen on cross section Partially organized clotted blood was frequently found adherent to the luminal surface of the intima at the level of stenosis and often there was a thrombus in the concavity immediately distal to the projecting intimal edge of the more pronounced stenoses

Cross sectional measurements of resected specimens from both symptomatic and asymptomatic patients on comparison with cross section areas of normal arteries demonstrated fairly consistently that the lumen of a major artery must be reduced by at least 90% to produce ischemic symptoms The relative ease with which endarterectomy can be done for stenotic lesions and the probability of eventual complete oc clusion if treatment is delayed strongly indicate that early surgery should be performed

Precipitating Factors in Venous Thrombosis are analyzed by J C Paterson and John McLachlin[5] (Univ of Western Ontario) through dissection and examination of the leg veins of middle aged or elderly patients 165 of whom died in the hospital Of these 72 (44%) harbored definite thrombi that were discovered on examination of the veins on each side from the lower end of the inferior vena cava to the posterior

(5) S g Gyn & Ob t 98 96-10 J ry 1954

Use of Dioxyline Phosphate in Peripheral Vascular Disorders has proved fairly successful according to Ralph A Deterling Jr[3] (Columbia Univ Presbyterian Med Center) who administered 200 mg doses of this papaverine derivative orally with meals and at bedtime often doubling the dose after three days More than 130 patients most with symptoms of peripheral arterial disease or phlebitis were studied from December 1949 to December 1952 Objective testing included a record of significant changes in skin color and warmth decrease in tenderness on pressure alterations in pulse or oscillometric readings and effects on specific lesions After dramatic subjective improvement a placebo was sometimes substituted for the drug and symptoms returned proving that the drug was providing relief

In acute arterial embolism or thrombosis evaluation of the drug was confused by the concomitant use of anticoagulants elevation of the head of the bed Buerger s exercises and occasionally surgery However the author felt that with the additional benefit of dioxyline phosphate (paveril®) patients did fully as well without toxic or side reactions as those who took papaverine or other antispasmodic drugs Patients with acute thrombophlebitis generally improved although the administration of anticoagulants 24 hours after the initiation of dioxyline treatment made interpretation of *results difficult Best results were evident with the* postphlebitic syndrome which permitted follow up of prolonged use of the drug Results were generally better if vasospasm played a greater part

Side effects (weakness and dizziness noted in three patients) were rare and mild

The drug given intra arterially to two patients with acute arterial embolism or thrombus brought no change in arterial pressure after a single dose of 100 mg —an important consideration when the maintenance of strong arterial pressure may prevent extension of the coagulum

Recognition and Treatment of Arteriosclerotic Stenosis of Major Arteries may preclude the serious consequences of arterial thrombosis which often follows symptomatic stenosis Edwin J Wylie and Joseph S McGuinness[4] (Univ of Califor

(3) A g I gy 4 397 405 O t b 1953
(4) S g Gy ec & Ob t 97 4 5 433 Oct be 1953

fatal In the period of study 5 467 patients were observed 12 cases of pulmonary embolism occurred of which 3 were fatal One of the three who died had pre existent phlebothrombosis and pulmonary infarction Another a woman did not wear the elastic stockings at any time In the third an elderly man thrombi in the prostatic plexus were found at autopsy but none were present in the calves or thighs Only three of the nine patients with nonfatal pulmonary embolism actually wore the stockings Thus the routine application of elastic stockings materially decreased the incidence of pulmonary embolism

It is believed that elastic stockings reduce the caliber of the venous channels and thereby increase the velocity of flow They should not be worn by patients with severe local disease in the legs—ischemia inflammation or trauma—and are probably contraindicated if phlebothrombosis already exists Proper treatment for venous thrombosis is anticoagulant therapy with or without venous ligation Elastic stockings though not a treatment for thrombosis can be important along with muscular exercise early ambulation etc in preventing pulmonary embolism

Vitamin B_1 Deficiency Mimicking Thrombophlebitis in Postoperative and Postpartum Period is discussed by Ben Eiseman[7] (Univ of Colorado) Among the earliest manifestations of thiamine deficiency are pain and tenderness in the lower extremity a manifestation of peripheral polyneuritis causing lesions that initially affect nerves and muscles of the calf and the anterior tibial group Since operations parturition and lactation all increase the need for thiamine such stresses may uncover latent subclinical thiamine deficiency Swelling and tenderness in the legs and calves Homans sign and tachycardia—manifestations of thiamine deficiency—can closely imitate thrombophlebitis at a time when both conditions are likely to occur

Although pain and tenderness accompany thiamine deficiency the heat and swelling characteristic of phlebitis are not present Enlargement of the circumference of the calf may occur in thiamine deficiency but is not so prominent as in most cases of thrombophlebitis The tachycardia of thiamine deficiency tends to appear gradually whereas that sec

(7) S g y 34 863 866 Nov mbe 1953

tibial vein at the level of the internal malleolus Serial sections were made of 21 tiny incipient thrombi found in an evaluation of the theory of local injury to the vessel wall

Antemortem determinations of factors in blood coagulability were correlated with the presence or absence of thrombi in patients who came to autopsy In varying numbers of patients no correlation was found between the presence of thrombi and the antemortem levels of antithrombin blood fibrinogen and fibrinogen B alpha tocopherol fibrinolysin and (in a small group) platelet count

Serial sections of the small thrombi failed to show any significant changes in the underlying vessel wall Phlebosclerosis was no greater when thrombosis was present when thrombosis did occur it was just as likely to appear at an area of less sclerosis Inflammatory infiltration—slight spattering with lymphocytes—was present in 30% of the patients with thrombi and in 12% of those without but bore no apparent relationship to the site of attachment

It was noted however that 80% of the tiny thrombi originated in the culdesacs formed by valve pockets which would be expected to be areas of stagnation of the blood Large thrombi also appeared primarily to be attached to the wall in the valve pockets The authors postulate that histologically indiscernible intimal damage occurs with stagnation of overlying blood leading to primary thrombus deposition and that prophylaxis against phlebothrombosis in the lower extremities depends on preservation of efficient venous return

Elastic Stockings in Prevention of Pulmonary Embolism II Progress Report *As a sequel to a previous study* using the alternate case method Robert W Wilkins and Joseph R Stanton[6] (Boston Univ) had every patient over 20 who was hospitalized more than 24 hours fitted with elastic stockings to be worn at all times except when bathing A 10 month period when no one was fitted with elastic stockings served as the control Only 6 3% either could not or would not wear the stockings They are included in the series however for the purpose was to show the over all effect of requesting the wearing of stockings routinely by all patients

During the control period (with 4 450 cases studied) there were 21 cases of pulmonary embolism of which 7 were

(6) New E gl d J M d 248 1087 1090 J ne 25 1953

Intermittent Claudication of Hip and Syndrome of Chronic Aortoiliac Thrombosis Victor G deWolfe Fay A LeFevre Alfred W Humphries Malin B Shaw and George S Phalen[9] (Cleveland Clinic) report on 47 patients with intermittent claudication each of whom was found to have stenosis or occlusion involving one or both iliac arteries or the lower abdominal aorta Most of the patients were men About half had no symptoms referable to the calf or any part of the leg The presence of trophic changes was unusual and impotence occurred in only one patient Aortography is invaluable in diagnosis and is easily performed with little morbidity

Differential diagnosis includes hypertrophic arthritis localized fibrositis or nonsuppurative bursitis (accompanied by tenderness) and a protruded lumbar intervertebral disk The last condition is associated with sensory and reflex changes and pain is typically aggravated by bending lifting coughing or straining

Treatment of thrombosis of the terminal aorta and iliac arteries is in its infancy Endarterectomy has few advocates and is followed frequently by recurrence Bilateral sympathectomy is sometimes helpful Autograft technics are being devised In the authors experience the lesion is not inevitably progressive as has been previously reported and they feel that conservative nonoperative treatment is justified in all but the more incapacitated patients

Intermittent claudication of the hip is rarely described or recognized yet is pathognomonic of arterial occlusion above the inguinal ligament

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THE KIDNEY

Determination of Function of the Individual Kidney can be accomplished accurately by evaluation of endogenous creatinine clearance according to Tom E Nesbitt[1] (Univ of Michigan) It has been shown that impairment of glomerular filtration function is almost universally accompanied by concomitant tubular disease Creatinine clearance reliably indicates degrees of deterioration in renal function in the presence of renal disease whereas other clinical tests become pro

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(9) C cul t 9 t 16 J cy 1954
(1) J U l 71 407-411 April 1954

ondary to thrombophlebitis is sudden in onset and evanescent Changes in the tendon reflexes with thiamine deficiency are unreliable The most helpful differential diagnostic point is the clinical response to large doses of thiamine Pain and tenderness will disappear within a few days in a patient with acute thiamine deficiency

Hemopericardium Associated with Anticoagulant Therapy Patrick A Izzo Richard C Stevens, A J Tomsykoski (Binghamton N Y) and Carlos E Rodriguez[8] (Wilkes Barre Pa) report three cases of this complication Its incidence is unknown but in 228 replies to a questionnaire sent out by Russek and Zohman to medical specialists 20 deaths presumed to have been due to hemopericardium were reported The authors three patients had myocardial infarction a few hours before coming to the hospital Two were treated with bishydroxycoumarin and one with ethyl biscoumacetate (tromexan®) prothrombin activity was apparently satisfactorily controlled although one patient was unusually sensitive to bishydroxycoumarin and on occasion the prothrombin activity fell to 12% of normal In the other two patients prothrombin activity did not fall below 17% In two patients substernal and epigastric pain developed suddenly on the 15th and 16th hospital days respectively the third patient apparently had a recurrence of chest pain within a week after hospitalization which became more severe on the 23d day cervical vein distention and hepatomegaly were evident A constant laboratory finding was a rather acute anemia coincident with development of hemopericardium No pericardial paracenteses were performed One patient died and at autopsy there was 600 cc of partly clotted blood within the pericardial cavity A diffuse serosanguineous film was attached to the posterior wall of the left ventricle over an area of recent infarction but there was no evidence of actual perforation

The occurrence of hemopericardium in these circumstances should be suspected in the presence of (1) recurrence of precordial pain after a pain free interval (2) circulatory collapse with hypotension hepatomegaly and distended neck veins of relatively sudden onset (3) sudden anemia and (4) roentgen evidence of pericardial effusion

(8) A.M.A. A h Int. M d 92 350 356 September 1953

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(9) C cul t 9 1 16 J ry 1954
(1) J U l 71 407-411 April 1954

gressively less reliable as renal impairment continues Normal 24 hour creatinine clearance is 125 150 L Comparison of the creatinine clearances of the two kidneys will often materially aid in the decision for or against nephrectomy

TECHNIC—After the patient is on a meat free diet for 48 hours ureteral catheters are passed and 30 minute specimens are collected from each kidney Venous blood is also drawn and the 30 minute endogenous creatinine clearance can readily be calculated for each kidney This value is extrapolated to a 24 hour clearance and compared with a 24 hour clearance determined on a voided specimen obtained either before or after instrumentation This serves as a check on the accuracy of determinations

Bright's Disease Attempt at Statistical Assessment of Classification Proposed by Ellis True nephritis defined by Osler as bilateral nonsuppurative inflammatory disease of the kidneys is one of the three main groups of Bright s disease the other two being chronic pyelonephritis and hypertensive nephrosclerosis Ellis has suggested that nephritis can be divided into two types Type I is characterized by hematuria of abrupt onset often preceded by an acute infection such as a sore throat Recovery usually follows adequate treatment but death may occur in the acute stage or several months later Other patients may appear to recover completely but years later have renal failure and hypertension Type II is of insidious onset with no history of antecedent infection Edema and albuminuria are common although hematuria is not This type is fatal with death from secondary infection hypertension or renal failure Ellis further suggested that these two types are clinically histologically and etiologically distinct

J B Enticknap and C L Joiner[2] (Guy s Hosp London) report on 154 fatal cases of nephritis and evaluate the validity of Ellis classification in an additional series of cases Data on the cases studied were from the hospital records few patients had been seen by either author Clinical diagnoses were made by one author on the basis of ward records and pathologic diagnoses by the other author independently after examination of autopsy material In 27 cases the data were inadequate or the diagnoses irrelevant (as toxemia of pregnancy polyarteritis nodosa etc) In 108 of the other 127 the authors agreed on the diagnosis It was found that acute type I nephritis pyelonephritis and nephrosclerosis could be

(2) B r M J 1 1016 10 0 May 9 1953

rather accurately diagnosed on clinical and pathologic grounds but there was only 63% agreement in chronic type I and type II cases Pathologically types I and II lesions can coexist in the same kidney On clinical grounds as well there was considerable overlapping The authors concluded that in the differentiation of nephritis the categories proposed by Ellis lack precision and the previous classification into acute subacute and chronic forms is justified

Age Differences in Renal Tubular Response to Antidiuretic Hormone were studied by John H Miller and Nathan W Shock[3] in 29 men ages 26-86 who had neither cardiovascular nor renal disease Water diuresis was established by administration of 250 cc water at 30 minute intervals Oral fluid intake was supplemented by intravenous injection of 8 cc /minute of 5% dextrose in water with inulin and sodium p aminohippurate added as indicated The infusion begun three hours after the beginning of the experiment was continued for 40 minutes before the start of the first urine collection period There were three control urine collection periods each 12 minutes long to begin with then after 0 5 mU /kg pitressin® was given intravenously six consecutive urine collection periods each lasting 12 minutes followed

Water diuresis was maximal as judged by absolute U/P inulin ratios during control periods and the constancy of the inulin values during the 36 minute control period in all but a few of the test subjects No significant difference was noted in control U/P inulin ratios among the young group (mean age 34 6 years) the middle group (mean age 54 9) and the old group (mean age 73 3) After administration of pitressin® prompt oliguria was noted in all groups Highly significant differences in U/P inulin ratios were noted between the young and middle and between the middle and old groups The negative correlation between age and the maximal U/P ratio after pitressin® suggests impairment of osmosis of the distal tubule in the older person

Acute Renal Failure John P Merrill[4] (Peter Bent Brigham Hosp Boston) stresses that the first step in treatment is to determine whether the lesion is promptly remediable Acute renal failure caused by shock cardiac failure dehydration

(3) J G tol 8 446 450 O t b 1953
(4) G P 7 55 62 J 1953

gressively less reliable as renal impairment continues Normal 24 hour creatinine clearance is 125 150 L Comparison of the creatinine clearances of the two kidneys will often materially aid in the decision for or against nephrectomy

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(2) Brit M J 1 1016-1020 May 9 1953

Electrolyte losses from vomiting can be replaced by equal volumes of a solution containing one half physiologic saline and one half glucose and water Losses from the lower intestinal tract could contain sodium bicarbonate in higher proportion than sodium chloride Potassium solutions should never be used in treatment of the patient with acute renal failure Hyponatremia and hypochloremia may be due to excess water retention or to deficit of the electrolytes A practical therapeutic approach is observation of the effects of restriction of water and administration of 250 300 cc of 5% sodium chloride Continuation of this therapy can be decided on by the clinical and laboratory response

For caloric needs 100-200 Gm glucose in 50% solution should be given through a plastic catheter in the femoral vein This averts the difficulties of oral feeding in the nauseated patient and minimizes the likelihood of thrombosis

Adjuncts such as testosterone propionate 25 mg /day control of infection (which causes increased protein breakdown) and oral digitalization for pulmonary edema are important Dialysis is beneficial and often lifesaving but never a substitute for good conservative care

Potassium intoxication a common complication is most likely when there has been infection necrotic tissue or accumulations of blood Resins are beneficial as is dialysis An emergency measure is infusion of 3 5% sodium chloride or bicarbonate another is infusion of 15 25% glucose with 1 unit of insulin/2 Gm glucose

The recovery phase generally supervenes within three weeks The last clinical evidence of function to return to normal is ability to concentrate the urine

Chronic Renal Failure results in uremia acidosis water and electrolyte abnormalities and may terminate in potassium intoxication The common hopeless attitude toward this disease is scarcely justified according to Arthur J Merrill[5] (Emory Univ) who outlines the major pathophysiologic derangements and treatment of chronic renal failure

Acidosis in renal failure is common because the catabolic end products are acid and the kidney cannot excrete them There may be a rather pronounced lack of symptoms of acidosis Alkalosis is uncommon and is usually iatrogenic it may

(5) Am P t & D g t T eat 4 679 685 Oct be 1953

electrolyte depletion heavy metal poisoning obstruction of the urinary tract and bacterial endocarditis may be corrected by immediate specific remediable measures Other causes of acute renal failure are carbon tetrachloride intoxication especially when associated with alcoholic intake acute glomerulonephritis with anuria or oliguria and absorption of distilled water through the prostatic bed during transurethral resection

Preliminary treatment consists of rectifying amenable disorders as far as possible Blood plasma or suitable electrolyte is administered early in oliguria from shock and dehydration Bichloride of mercury poisoning is promptly treated with BAL Alkalinization of the urine may be desirable in renal failure due to intravascular hemolysis Although the rationale of the latter procedure implies that the significant lesion here is precipitation of acid hematin in the tubules which is not the sole cause still it may be a valid procedure if one remembers that alkalinization of the urine following administration of sodium bicarbonate or lactate solution depends on some degree of adequate renal function Administration of 6-8 Gm sodium bicarbonate will be sufficient if renal function is adequate if it is not no amount will be beneficial and over loading will occur Intravenous administration of procaine lumbar sympathetic block spinal anesthesia and renal decapsulation are of questionable benefit and the incident trauma is deleterious

Average duration of the anuric phase is 5 10 days and its treatment can be divided into four categories (1) replacement of water (2) replacement of electrolytes (3) provision of calories and (4) therapeutic adjuncts Replacement of water can be based on an estimated 0 6 cc /hr /kg of insensible water loss with suitable correction made for high environmental temperature To the figure obtained should be added the volume of the previous day s urine plus other losses as from vomiting and diarrhea From these figures should be subtracted 300 500 cc /day as equivalent to the water produced by the oxidation of food It is important to maintain accurate weight records for these patients A gain of weight in the presence of inadequate caloric intake or over a longer period failure to lose weight with inadequate caloric intake indicates water overload

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(5) Am P ct. & D g t T eat 4 679-685 Oct ber 1953

be produced with 2-4 Gm sodium bicarbonate daily There may be hyperosmolarity of the extracellular fluid or simple extracellular fluid deficiency Water intoxication may also develop

Potassium intoxication is common terminally and is manifested by ECG changes (peaking of the T waves followed by disappearance of the P waves and delay in intraventricular conduction time) as well as by lethargy weakness nausea confusion and convulsions Potassium deficit is uncommon but may occur with pyelonephritis High blood calcium level is rare and is most likely due to hyperparathyroidism with secondary renal tubular calcification Low blood calcium level is very common because of poor intestinal absorption acidosis with loss of calcium as a base and high blood phosphorus content In hypocalcemia the S T segment of the ECG is prolonged without change in the T wave and clinically there may be tetany with carpopedal spasm and convulsions Fractures and pseudofractures may occur Blood phosphorus content is usually high unless the filtration rate is adequate The low calcium concentration in the blood stimulates the parathyroid glands which will normally cause increased excretion of phosphorus With a depressed filtration rate this cannot occur and phosphorus level remains high thus prohibiting homeostatic elevation of the blood calcium Bony deformities and fractures occur

Salt losing nephritis fails to respond to desoxycorticosterone acetate and is thus differentiated from Addison s disease It is rare although there are many patients with hyponatremia because of acid base adjustment Potassium losing nephritis is likewise rare and in this disease the tubules are unable to reabsorb filtered potassium Renal rickets (tubular insufficiency with glomerular insufficiency) results in hypocalcemia becau e of the chronic acidosis and the blood phosphorus level rises because the filtration rate is too low to permit increased excretion of phosphorus In Milkman s disease (tubular insufficiency without glomerular insufficiency) the calcium level falls similarly but glomerular filtration being essentially normal can dispose of the increased phosphorus load and a low blood phosphorus level results The compensatory action of the parathyroids brings the blood calcium back to near normal but the decalcified bones are brittle and often

break Since osteoid formation is normal the fractures heal without calcification producing pseudofractures In the Fanconi syndrome calcium loss is due to a basic inability of the tubules to reabsorb sugar The liver becomes depleted of glycogen and chronic acidosis from catabolic products of fat produces calcium depletion Phosphate and amino acids are lost also but do not figure in the calcium depletion

General treatment includes (1) protein intake of 20 Gm daily (2) high carbohydrate and moderate fat intake to prevent body protein breakdown (3) salt intake of 4-5 Gm daily (4) sodium bicarbonate as a source of sodium instead of salt when acidosis is present (5) potassium administration only when a deficit is obvious and when urinary output is adequate (6) calcium intravenously during emergencies since alimentary absorption is poor (7) omission of phosphorus and sulfate containing foods and use of aluminum hydroxide orally to increase loss of phosphorus and sulfate in the stool and (8) transfusions as necessary for anemia

Three laboratory tests provide an appraisal of the kidney function urea clearance or blood nonprotein nitrogen level as a measure of filtration efficiency phenolsulfonphthalein excretion or maximum tubular excretory capacity measurement to evaluate proximal tubular function and urine concentration test to evaluate distal tubular function

Problems in Maintenance of Chronic Bilaterally Nephectomized Dog are discussed by C Riley Houck[6] (Univ of Tennessee) who maintained 15 such dogs with low salt diet peritoneal dialysis and transfusions One was kept alive 111 days The diet was a modification of the low salt diet proposed by Grollman peanut oil content and polysorbate intake were reduced ferrous sulfate was eliminated and Celluflour added for bulk Vomiting and diarrhea were less frequent with this diet Vomiting was thought to be related to dehydration and azotemia Dialysis with 1 500 2 000 cc of 0 75% glucose and electrolytes two or three times daily with occasional administration of 5% glucose or saline intravenously maintained proper hydration Plasma sodium chloride and potassium levels usually remained within normal limits although there was occasional hypokalemia which was corrected as necessary by addition of 300 mg potassium chloride to each 2 L dialysis

(6) Am J Phy 1 176 175 18 F bru y 1954

fluid Plasma nonprotein nitrogen creatinine and total phenol levels remained moderately elevated and appeared to exert no particular toxic effect Plasma proteins were regenerated as rapidly as they were removed by dialysis All dogs had anemia and those living a week or longer had hypertension Frequent transfusions of saline suspended cells were given Blood volume remained fairly constant but plasma volume increased in most instances

Autopsy revealed enlarged adrenal glands in 10 dogs and generally enlarged lymph nodes in 8 4 had enteritis 3 detached retinas thought to be the result of hypertension 3 left ventricular hypertrophy and 3 intestinal intussusception

Peritoneal Dialysis as Means of Detoxication in Uremia and Other Toxic Conditions Peritoneal dialysis according to H Henninger[7] (Vienna) is a relatively simple method of substitutive therapy in renal failure and can be prolonged 20 days or more When the underlying renal disease is acute and reversible—as in some instances of mercury poisoning and hemoglobinuria—this procedure may adequately replace the electrolyte regulating functions of the kidneys long enough so that the patients can recover Another important indication for peritoneal dialysis is intoxication as with barbiturates when the imposition of this procedure may greatly enhance the removal of the poison from the blood

METHOD—Through a small incision in the right mesogastrium an inflow catheter was inserted so that its tip extended about 3 cm into the peritoneal cavity Another incision was made in the left hypogastrium and two catheters inserted into the culdesac so that the tip of one catheter lay 3 cm ahead of the tip of the other thus roofing it over to attempt to prevent its obstruction by omental adhesions Through the inflow tube irrigation fluid flowed at the rate of 1 L /hour and the larger part was recoverable through the outflow tubes The composition of the irrigation fluid was

Ringer s solution	1 000 cc
Dextrose	10
Heparin	0 1
Streptomycin	0 5-0 1
Penicillin	10 000 units
Sodium citrate (3 8%)	50

Of 17 patients treated with peritoneal dialysis many had far advanced and irreversible renal disease (chronic pyelonephritis amyloidosis of the kidneys bilateral purulent cysto

(7) J I t rn t C ll S rg o 19 533 547 M y 1953

pyelonephritis etc) but 5 survived with the aid of peritoneal dialysis One of these had corrosive mercuric chloride poisoning another had chronic nephritis with an acute exacerbation and three were poisoned with soporifics The last three were not in renal failure but peritoneal lavage increased the excretion of the toxic material large amounts of which were recovered from the irrigating fluid

Twelve of the 17 patients had renal disease and 7 of these were anuric Deaths occurred principally because of irreversible renal disease or superimposed complications such as pulmonary edema Even in these cases however there were noteworthy reductions of the nonprotein nitrogen level which remains the indicator of the extent of the uremia

Artificial Kidney XXII Dialytic Treatment in Four Selected Cases of Acute Glomerulonephritis, Contribution to the Question of Need for Dialysis in Rational Renal Therapy The present day conservative treatment of acute glomerulonephritis—embodying the concentrated caloric intake of butter and sugar oil and glucose 15% glucose intravenously with a total of at least 100 Gm glucose daily—may not be adequate to prevent death in uremic intoxication In a few cases dialysis may be lifesaving By dialysis of the blood the rapidly increasing nonprotein nitrogen often can be dramatically reduced and the level of consciousness alertness and comfort improved

Nils Alwall Anders Lunderquist and Axel Tornberg[8] (Univ of Lund Sweden) present data on four patients with acute glomerulonephritis and severe uremia All four showed profound subjective response with lowering of the nitrogenous content of the blood Two died despite dialysis and autopsy in each showed serious anatomic changes of irreversible renal disease These two patients were anuric 42 and 44 days The authors feel that although the eventual outcome was unchanged their lives were prolonged at least a month In two other patients who were anuric 7 and 11 days it seemed clear that dialytic treatment was the lifesaving measure inasmuch as a conservative regimen was proving inadequate The outcome in a particular patient with glomerulonephritis is impossible to foretell the extent of irreversibility cannot be determined clinically Dialysis should be considered as an ad

(8) Act med d 145 175 180 1953

junct to conservative treatment in rational renal therapy of acute glomerulonephritis

***Corticosteroids and Antidiuretic Substance in Nephrotic* Children** According to Enrique Galan Manuel Perez Stable Orlando Garcia Faez Emilio Unanue Otto Garcia Juan M Labourdette and Gilberto Alfonso[9] (Havana Med School) nephrotic edema may be partially dependent on increased tubular reabsorption On the other hand an increase in urine output may occur not only after an increase in glomerular filtration rate but also from decreased tubular reabsorption and with or without changes in filtration fraction An anti diuretic substance (ADS) found in the urine of edematous patients resembles posterior pituitary antidiuretic hormone (ADH) Urinary corticosteroids were determined by the chromotropic sulfuric reaction for formaldehyde The ADS was evaluated by intraperitoneal injection of blood urine or ascitic fluid in rats

Of four children with the nephrotic syndrome two had no symptoms of glomerular involvement two had hematuria and azotemia A patient with acute hemorrhagic nephritis was also studied and three patients were used as controls Nephrotic patients had low excretion of steroids during spontaneous increase in urinary volume and elimination of edema whereas the one with hemorrhagic nephritis had a rise of urinary ster oids during the same clinical event Two patients with corti cotropin induced diuresis had an increase in total steroid ex cretion in two with no diuretic response to the drug there was no increased steroid excretion Urinary volume and uri nary steroid excretion were correlated in nephrotic children but not in controls Both nephrotic and normal children ex creted steroids in relation to the urine volume/glomerular filtration rate ratio suggesting participation of tubular re absorptive processes in the excretion of steroids Formalde hydogenic steroids did not appear to have a direct role in producing variations of urine flow in nephrotic children

Serum antidiuretic substance apparently closely correlates with antidiuresis The ADS appeared to be present in the globulin fraction of plasma proteins No antidiuretic effect was noted with intraperitoneal injection of plasma albumin protein tree filtrate and ascitic fluid An increase in titer of

(9) P d at cs 1? 33 Sept mb r 19 3

ADS was observed during initial doses of ACTH and the reverse at the onset of diuretic response

Renal Excretion of Creatinine and Inulin in Man Studies designed to clarify the relationship between the clearances of inulin creatinine and creatinine chromogen and to re examine the methods of excretion of these materials are reported by Emanuel E Mandel Florence L Jones Myron J Willis and Walter H Cargill[1] (Emory Univ)

METHODS—The clearance technics of Smith were used Inulin was determined by the resorcinol method para aminohippurate (PAH) by the method of Smith and collaborators and creatinine was measured by Hare s adsorption-elution method Clearances of inulin (C_{IN}) and creatinine (C_{CR}) were determined concomitantly in 13 subjects with normal kidneys (with normal plasma creatinine levels up to 1.2 mg /100 ml) and in 21 patients with renal disease whose plasma creatinine levels were 0 77 15 4 mg /100 ml

Among the normal subjects the mean C_{CR} C_{IN} ratio was very slightly above 1 0 whereas the range of extremes and the differences among the subjects were considerable From the data it is shown that the error in predicting C_{IN} from C_{CR} can be quite large but it will be less than 7 5% of the actual C_{IN} value about two thirds of the time On the other hand creatinine chromogen clearance (C_{CHR}) values averaged 24% lower than the corresponding C_{IN} values

In the patients with renal disease the mean C_{CR} and C_{CHR} were 25 and 29% greater than the corresponding C_{IN} values The range of C_{CR} C_{IN} values in this group was 0 72 1 83 The lack of homogeneity of the group precludes further statistical analysis However the C_{CHR} C_{CR} ratio in normals was 0 71 and in the patients with renal disease was 0 94 The range in this ratio was no wider in the patients than in normal subjects

Inulin clearance had no relation to variations in plasma inulin levels (P_{IN}) which were unavoidably encountered during the procedure Deliberate changes in plasma inulin level were shown to have no effect on C_{IN} C_{PAH} C_{IN} or in the proportionality between P_{IN} and the rate of inulin excretion

Although the experimental error (coefficient of variation) in the inulin and creatinine clearance measurements was 8 3 10 1% this corresponds well with similar estimations by others and the coefficients though considerable in magnitude

(1) J Lab d Cl M d 42 6 1 637 October 1953

were practically the same for creatinine and inulin clearances Therefore however large the fluctuations of C_{CR} and C_{IN} may be in a subject they usually occur in the same direction and are of similar magnitude so that fluctuations of ratios from period to period are proportionately not greater than those of clearances Thus the inference may be that the wide range of ratios encountered in the normal group and the large standard deviations of these ratios between subjects cannot be explained by chance alone This observation is consistent with theoretical differences in excretion mechanisms for the two substances and the occasional equality of the two clearances is ascribed to chance The far wider range and higher mean value of C_{CR} C_{IN} in subjects with renal disease in this and in other series appears to emphasize the difference in excretion mechanisms of the two substances under pathologic conditions

Since inulin clearance remained independent of plasma inulin concentration the authors suggest that tubular transfer usually plays no role in the excretion of inulin but that it is operative in the excretion of creatinine in the form of tubular secretion or reabsorption or a possible combination of both in health as well as in disease or (in line with Chinard s concept of glomerular filtration) that the difference in clearance may be caused by gradients in chemical potential molecular size and electrical potential The authors conclude that in health the endogenous creatinine clearance appears to be an acceptable clinical substitute for inulin clearance but in renal disease it is a poor measure of glomerular filtration rate The creatinine chromogen clearance normally is about 25% lower than the creatinine clearance but approximates the latter in patients with azotemia

Hexamethonium in Chronic Treatment of Hypertension Effect on Renal Hemodynamics and on Excretion of Water and Electrolytes is discussed by Ralph V Ford John H Moyer Charles L Spurr C Polk Smith and Georgia Weller (Baylor Univ)

METHOD—Seven patients with hypertension were studied by measurements of the glomerular filtration rate (GFR) renal plasma flow (RPF) and maximal tubular excretory capacity (Tm_{PAH}) Measurements were determined at rest and during ambulation before

( ) J Cl I t 3 1133 1139 N mb 1953

institution of hexamethonium therapy The patients were then given hexamethonium orally four times daily to establish a reduction in mean blood pre sure (MBP) of 40 mm Hg or more when in the upright position A second group of studies was done after a month or more of the drug therapy and after at least seven days of con sistent reduction of blood pressure

Hexamethonium produced an average reduction of MBP to 78% of the control in the supine position which was not associated with significant change in the GFR Tm_{PAH} or RPF The constancy of renal blood flow associated with a reduction in mean blood pressure was reflected by an average decrease in renal vascular resistance (RVR = MBΓ/RBF) of 28%

During ambulation before institution of drug therapy there was no alteration in MBP but there was evidence of renal vasoconstriction shown in a depression of the GFR RBF and Tm_{PAH} and an increase in the RVR Ambulation after hexamethonium was given caused an additional reduc tion of the MBP from 78% to 65% of the control supine value associated with renal vasoconstriction and reduction in GFR RPF and Tm_{PAH} more marked than before use of the drug

Before administration of the drug ambulation caused a reduction in urine volume and sodium excretion to 79% and 75% of the control supine observations respectively without a reduction in blood pressure After ganglionic blockade and blood pressure reduction with hexamethonium ambulation further decreased blood pressure associated with a sharp re duction in urine volume and sodium excretion of somewhat greater magnitude percentagewise than during the control period There was no change in the potassium excretion due to ambulation during the control period but after hexameth onium there was an apparent decrease to 79% of the supine value during hexamethonium therapy All patients but one had a reduction in serum sodium content during the month of therapy with hexamethonium

The authors conclude that the previously demonstrated changes in GFR RPF and Tm_{PAH} in response to parenteral therapy with a single dose of hexamethonium hold also during chronic oral therapy The kidney retains vasoconstrictor mechanisms in response to posture even after ganglionic blockade with hexamethonium

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Hypertensive Phase of Acute Nephritis Specific Therapy with Derivative of Veratrum Viride Acute nephritis of childhood has shown little variation in incidence despite the increased use of antibiotics early in the treatment of streptococcic infections The two complications which contribute most to its impressive mortality in early stages are heart failure and encephalopathy both may be partly the result of rapid rise in blood pressure No single agent has proved entirely satisfactory over the years Stephen W Royce[3] (Univ Southern California) discusses the use of alkavervir (veriloid®) a standardized mixture of alkaloid esters of Veratrum viride in six children Its effects are three (1) hypotensive achieved by generalized vasodilatation and mediated through the central nervous system being neither sympatholytic nor adrenergic blocking (2) myocardial causing increase in cardiac output with bradycardia through a vagal action and (3) renal with vasodilatation and initial decrease in renal blood flow followed by quick return to or above normal

METHOD—After base line blood pressure readings ECG blood chemistry determinations and clinical observations were made the drug was given intravenously over 20 minutes in a dosage of 0 022 cc veriloid® solution/kg body weight diluted to 10 cc with 5% glucose solution Following this a maintenance infusion was given with 0 13 cc veriloid®/kg in a total solution of 22 cc /kg in 5 or 10% glucose running at a rate of 5 drops/10 kg minute The amount of the rapid infusion and the duration of maintenance therapy were determined by the hypotensive response of the patients In general a blood pressure decrease of about 20 mm Hg was sought and return to normal levels was not considered necessary or desirable Ephedrine 1% and atropine 1 1 000 were kept available as antidotes for extreme hypotension or bradycardia respectively

In this small series of six patients results were uniformly good No instances of toxicity were observed two patients had mild nausea and one vomiting During a minimum of two years follow up they remained well and normotensive

Innate Functional Defects of Renal Tubules, with Particular Reference to Fanconi Syndrome Cases with Retinitis Pigmentosa It has been previously hypothesized that in the multiplicity of tubular functions there may be uni or multifactorial innate defects, resulting in numerous syndromes of renal dysfunction W P U Jackson and G C Linder[4] (Univ

(3) Ped tri s 12 358 367 Oct b 1953
(4) Qu rt J Med. 22 133 156 Ap l 1953

of Cape Town) enumerate the inherent defects and the symptoms which result

Unifactorial

Deficient reabsorption of	
Water	Renal diabetes insipidus
Phosphate	Vitamin D resistant rickets
Glucose	Renal glycosuria
Cystine and other amino acids	Simple congenital cystinuria
Amino acids	Hepatolenticular degeneration
Calcium	Idiopathic hypercalcuria
Bicarbonate	Hyperchloremic nephrocalcinosis
Excessive reabsorption of	
Phosphate	Pseudohypoparathyroidism

Multifactorial (probably all one disease the Fanconi group)

Deficient reabsorption of	
Phosphate and sugar	Glycosuric rickets or osteomalacia
Phosphate sugar and amino acids	Fanconi syndrome

(*often associated with inability to reabsorb water albumin* (?) and fixed base and to form ammonia glomerular defect and organ cystinosis)

All of these conditions of primary deficiency of tubular function are inherited abnormalities except hyperchloremic nephrocalcinosis of which no more than one case has been reported in any family

The syndrome named after Fanconi comprises essentially vitamin D resistant rickets with low serum phosphate level normal serum chloride level glycosuria and aminoaciduria Frequently there are albuminuria chronic acidosis and neutral or alkaline urine with a high ammonia content Cystine deposition in internal organs is frequent The disability is severe and ends in glomerular failure or hepatic cirrhosis and death One hypothesis is that there is a fundamental failure of the proximal tubules to reabsorb bicarbonate from the glomerular filtrate the presence of a high bicarbonate concentration in the distal tubules inhibits the formation of ammonia and when the normal exchange of hydrogen for basic ions in the tubules takes place a large amount of carbonic acid is formed

The authors discuss the multiple tubular dysfunction syndrome as it occurred in four patients A boy 10 had *hypophosphatemic glycosuric rickets and infantilism albumi*

nuria slight aminoaciduria acid urine hypocalcuria and reduced production of ammonia in response to acid ingestion Renal phosphate clearance was high There was considerable reduction of glomerular function He was mentally backward and a deaf mute and had gross pigmentary retinal degeneration His sister 4 had the same aural and ocular conditions and showed similar biochemical abnormalities to a much smaller degree She did not have hypophosphatemia glycosuria or rickets The third patient a girl 13 with glycosuric rickets osteoporosis and infantilism had increased organic acid and amino acid excretion with defective ammonia production She also had hypophosphatemia polyuria (resistant to pitressin®) and retinitis pigmentosa Her sister who had not been adequately investigated before death at age 22 undoubtedly had had the Fanconi syndrome She also had had retinitis pigmentosa These four patients with the multifactorial tubular defects all had pigmentary retinal degeneration The authors suggest that a hitherto undescribed recessive gene complex produces this picture

Renal Function Studies in Adult Subject with Fanconi Syndrome are reported in detail by Jonas H Sirota and David Hamerman[5] (Mount Sinai Hosp New York City)

Man 54 had weight loss glycosuria proteinuria weakness and low back pain for at least seven years Glucose tolerance curve was normal initially but subsequently became diabetic Low serum inorganic phosphate and elevated serum alkaline phosphatase level hyperchloremic acidosis and hyperaminoaciduria with normal plasma amino acid concentration were noted For four years he was bedfast and there was further deterioration in renal function X ray studies revealed decalcification and pseudofractures Bence Jones protein was repeatedly observed several years after onset of symptoms and bone marrow aspirate showed 8 14% multinucleated plasma cells consistent with the diagnosis of multiple myeloma which was believed to be unrelated to the renal disease

Renal clearance studies showed disproportionate reduction in several modalities of proximal tubule activity as compared with glomerular function Glomerular filtration rate (inulin and creatinine clearances) was 32% of the expected normal but the clearance of p aminohippurate (C_{PAH}) Tm_{PAH} and Tm_G were about 7% of the expected normal A greatly depressed plasma urate concentration (1 7 mg /100 cc) was probably the result of complete failure of proximal tubular reabsorption of filtered uric acid Inorganic phosphate clearance was high (25 7 cc /minute) presumably another

(5) Am J Med 16 138 152 Jan 2 7 1954

manifestation of failure of the proximal tubules Renal excretion of amino acids was 1,300 mg /24 hours (normal 200-400 mg) Urinary bicarbonate was excessive despite systemic acidosis Capacity for phenol red excretion was greatly depressed

Renal function deteriorated steadily during the five years for which data were vailable (Values given are corrected to 1 73 sq m) Glomerular filtration rate declined from 55 7 to 26 5 cc /minute The Tm_G was 50 9 mg /minute this deteriorated to 26.3 mg Ability to form ammonium ions under maximal ammonium chloride induced acidosis fell from 34 6 mEq /day in 1947 to 11 1 in 1952 The urine pH could be lowered to 5 initially four years later the lowe t attainable value was 6.2 The C_{PAH} fell from 43 8 to 26 5 cc./minute in one year The depression of glomerular filtration gradually reflected itself in increasing plasma concentrations of urea creatinine uric acid and inorganic phosphate

Infantile Renal Acidosis, counterpart to adult hyperchloremic acidosis thought to be caused by inability of the renal tubule to make ammonia is characterized by low plasma bicarbonate and elevated chloride values alkaline urine and nephrocalcinosis It usually occurs during the first 18 months of life R Lightwood W W Payne and J A Black[6] (Hosp for Sick Children London) discuss the disease as it was observed in 35 patients

Symptoms developing insidiously included failure to thrive irregular vomiting constipation and change in temperament Plasma chloride level was greater than 108 mEq /L in all but two cases and plasma bicarbonate was below 19 mEq /L Urine was less acid than would be expected from the degree of acidosis most specimens had a pH between 6 8 and 7 2 The most acid urine was pH 6 02 whereas an infant usually can produce urine with a pH of 4 8 5 0 following ammonium chloride acidosis

When present nephrocalcinosis was equally distributed bilaterally There was no evidence of calculi The deposition of calcium in the kidneys is considered to be the result of acidosis and hypercalciuria with precipitation in the tubules

Pyelitis Fanconi s syndrome idiopathic hypercalcemia vitamin D intoxication and diabetes insipidus may present similar pictures

Treatment was alkalinization by administration of 10 Gm sodium citrate and 6 Gm citric acid/100 cc water usually beginning with 15 cc four times daily Dosage was subsequently

(6) P d trics 12 6 8-644 Decemb 1953

adjusted to keep plasma bicarbonate at 18-22 mEq/L Treatment was gradually withdrawn when the bicarbonate value remained normal for several months and when the child was doing well All patients were cured

If the ability of the proximal tubule to absorb bicarbonate preferentially to chloride or the ability of the distal tubule to secrete hydrogen ions matures later than normal particularly later than glomerular filtration function the increased ouput of bicarbonate could cause acidosis

THE DIGESTIVE SYSTEM

FRANZ J INGELFINGER, M.D

PART V

THE DIGESTIVE SYSTEM

THE ESOPHAGUS

Peptic Stenosis of Esophagus Edward B Benedict and J E O N Gillespie[1] (Massachusetts Gen l Hosp) studied 60 males average age 56 8 and 40 females average age 60 1 with peptic stenosis of the esophagus of unknown origin All had dysphagia 42 vomiting and regurgitation 30 epigastric pain 17 odynophagia and 22 heartburn A surgical operation requiring anesthesia and hospitalization had been performed within five months before development of dysphagia in 22 and 15 of these had onset of dysphagia during convalescence

An esophageal hiatus hernia was definitely present in 85 and probably present in 2 Recorded average length of 20 hernias was 5 cm Definite x ray evidence of esophageal ulcer was present in 40 and doubtful evidence in 12 There were 40 with present or past duodenal ulceration and 4 with symptoms of ulcer but no x ray evidence Esophagoscopic biopsy revealed gastric mucosa in 49 and acute or chronic inflammation of esophageal mucosa in the rest Thickened periesophageal inflammatory tissue was present in 20 resected specimens and in 3 in which cardioplasty or repair of the hiatus hernia had been done In all cases the site of stenosis was the cardia or just above it In the two in which cardioplasty was done the stricture was a few millimeters thick in one and 1 5 cm in the other The esophagus was ulcerated in 17 of the 20 surgical cases One patient died of spontaneous perforation of the esophagus and another of rupture following esophagoscopy

Peptic stenosis of the esophagus is due to abnormally prolonged contact of gastric juice with the region above the cardia It can occur in a normal person but is more likely in those with the ulcer diathesis Gastric juice occurs in the lower esophagus to an abnormal extent as the result of an esophageal hiatus hernia of the sliding type and excessive vomiting

(1) S g Gyn c & Ob t 98 494 502 Ap l 1954

or regurgitation from relaxation of the cardia Ectopic gastric mucosa is probably not an important cause of peptic esophageal stenosis Regurgitation of gastric juice may occur during recumbency after surgery

The first method of treatment is bouginage which should always be done with a guiding thread Of 34 patients treated by bouginage and followed for at least a year after the last treatment 17 had good and 15 fair results and 2 were unchanged Mean number of bouginage treatments was 7 the range 1 54 The length of treatment was up to 13 years and 10 months

Surgery is indicated only if bouginage fails if there is severe hemorrhage or if there appears to be a risk of penetration of an ulcer Of 20 patients treated by resection and esophagogastric anastomosis or plastic operations 3 died *postoperatively 2 had recurrence of the stenosis 2* required pyloroplasty after resection and of the other 13 only 9 were alive without dysphagia Nevertheless resection and esophagogastric anastomosis may be a very good operation since in 11 of 12 patients followed over one year results were classified as good Some patients with good results had a fair amount of fluid in the thoracic portion of the stomach seen by x rays but this did not appear to cause difficulties Of five patients having repair of a hiatus hernia without other surgery except for one with combined cardioplasty *three had* recurrence of the hernia

[The prevalence of hiatus hernia and duodenal ulcer in this group of patients provides substantial support for the theory that chronic stenosing esophagitis is another acid peptic disease It may be argued therefore *that patients requiring surgery for peptic stenosis and inflammation* of the esophagus should be offered a definitive ulcer operation (i e subtotal gastrectomy or hemigastrectomy with vagectomy) in addition to treatment of the local lesion of bouginage repair of the hernia or if necessary resection with esophagogastric anastomosis —Ed]

Insufficiency of Cardia in Hiatus Hernia Charles A Flood Josephine Wells and Daniel Baker[2] (Columbia Univ) studied 41 adults with radiologic evidence of hiatus hernia 37 of whom had symptoms referable to the esophagus In 18 of 34 patients reflux of barium from the stomach into the esophagus was *demonstrated radiologically The hiatus hernia was demonstrated* best when the subject turned from supine to prone position The incidence of reflux appeared to bear no

( ) G t oent ology 25 364-374 No ember 1953

relation to the angle at which the esophagus entered the stomach No esophageal reflux was noted in six control patients with surgically corrected hiatus hernias Only two of 100 controls had reflux Of 15 patients with hiatus hernia studied by esophagoscopy reflux of stomach contents into the esophagus was found in 8 Of 10 patients with hiatus hernia subjected to esophageal intubation reflux into the esophagus was noted in 5 Of 14 patients with hiatus hernia subjected to both x ray and esophagoscopy there was evidence of reflux by both methods in 9 Of 11 patients with esophagitis revealed by esophagoscopy reflux was noted in 6 The presence of esophageal stricture did not appear to influence the findings Of seven patients without esophagitis reflux was found in five

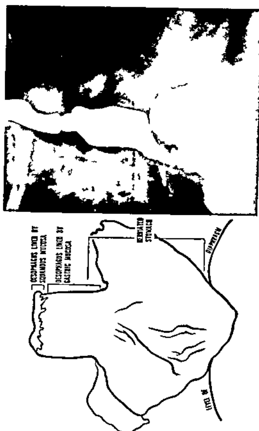
The study indicates that hiatus hernia is frequently accompanied by ulcerative esophagitis and that reflux is common with or without esophagitis Although regurgitation of acid gastric juice probably plays an important role in production of ulceration of the esophagus a correlation between reflux and esophagitis could be demonstrated by the methods used in this study in only about half the cases

[The lack of any con istently reliable maneuver for demonstrating gastroesophageal reflux in patients suspected of having this disorder is one of the problems encountered in establishing reflux peptic esophagitis as a definite clinical entity Turning the patient from supine to prone position is certainly as effective for demonstrating reflux as various methods designed to increase intra abdominal pressu e—Ed]

Esophagus Lined with Gastric Mucous Membrane The muscular tube lined with squamous epithelium and extending from the pharynx downward may be correctly designated as the esophagus According to P R Allison and A S Johnstone[3] a variable amount of this tube below the arch of the aorta may be lined with gastric mucosa This region has no peritoneal covering the musculature is that of normal esophagus islands of normal squamous epithelium may be present there are no oxyntic cells and in addition to gastric glands esophageal mucous glands are present The proper term for this probably congenital abnormality which looks like esophagus from the outside and like stomach from the inside would appear to be esophagus lined with gastric mucous membrane instead of stomach as described by Barrett

The authors report on seven patients with this type of

(3) Th 8 87 101 J 1953



F g 71 (l ft) —R ct d low ph gus d hern t d po t n of stoma h N rrow t p f q mo l g at top of soph gus s ffic ent t sh w phag t s
F g 72 (ght) —Sam ca y how g th gment T p gm t i I n d w th qu mo s ep th l m St tu f m fl x ph g t l t b l w ch of ort s p t fi st f m s nd s gme t ph gu l n d w th g t c m c m mb n C n t t on d by d a m ks t p f th d gm t st m h h t d bo d ph gm (C t y f All son P R d J h t A S Thor 8 87 101 J 1953)

esophagus all of whom had hiatus hernia It is not known whether this association is constant Peptic ulceration and esophagitis are quite common in this condition and are found at the lower limit of squamous epithelium Ulceration is superficial severe bleeding is uncommon and perforation does not occur There is dense submucous fibrosis leading to circumferential stenosis of varying length and degree Gastric ulcers in contradistinction may occur in the gastric mucosa lining the esophagus and when chronic might be referred to as Barrett s ulcers These lesions may cause stenosis or severe bleeding or may perforate with resulting subacute mediastinitis or

acute pleuritis They may be present alone or combined with reflux esophageal ulcers and unlike peptic esophageal ulcers may respond to medical management In both instances demonstration of the ulcer is difficult

In a simple sliding hernia the esophagus joins the stomach pouch at its apex Hernia is usually diagnosed radiologically by observation of a slight constriction at the cardiac junction The size of the pouch the mucosal pattern and the continuity with the rest of the stomach below the diaphragm are distinguishing features A criterion more important than that provided by the mucosal pattern however is the competence of the cardia to prevent gastric reflux When hiatus hernia and esophagus with gastric mucosa and peptic esophagitis with stenosis coexist a typical radiographic picture of three segments—normal esophagus esophagus with gastric mucosa and stomach—separated by the stricture and the cardia is seen (Figs 71 and 72) The segment between the stricture and the cardia is thought to be esophagus lined with gastric mucosa This conclusion rests on inference and not on a demonstrable change in mucosal pattern It may also be thought to exist when there is a significant difference between the level of mucosal change on esophagoscopy and the estimated level of the cardia by radiography

[This article goes to the heart of the problem the structure and function of the gastroesophageal junction are variable and not well understood. It is therefore helpful to be provided with a classification which distinguishes clearly between the two types of acid peptic lesion that involve respectively the two types of mucosa found at the gastroesophageal junction —Ed]

Surgical Management of Achalasia of Esophagus H R Hawthorne and Paul Nemir Jr [4] (Univ of Pennsylvania) performed esophagocardiomyotomy for cardiospasm on 22 patients and followed them for two months to five years In most patients no hypertrophy of the muscular layers was found A few had considerable hypertrophy of the longitudinal muscle fibers and occasionally of the inner circular muscle bundle

TECHNIC —The modified Heller operation consists of exposure of the cardioesophageal junction by division of the left triangular ligament of the liver and retraction of the left lobe down to expose the hiatal region Division of the peritoneal reflection permits retraction down and exposes the dilated esophagus A longitudinal incision is

(4) G t t l gy 25 349 358 N mbe 1953

then made in the anterior esophageal wall down to the mucosa and the edges are separated allowing the mucosa to bulge outward The incision is then extended in the cardia 1½ in and about 2½ in in the esophagus

Of the 22 patients 1 died postoperatively of cerebral vascular accident All the others were relieved of dysphagia 18 (86%) obtained excellent results with complete relief of obstruction could take a full diet and did not need dilatations About 50% of the patients studied fluoroscopically postoperatively had regurgitation when placed in the Trendelenburg position and subjected to the Valsalva maneuver All who had symptoms postoperatively also had regurgitation Postoperative complications included esophagitis and hemorrhage secondary to regurgitation in three cases

Although the results of esophagocardiomyotomy were impressive and the number of complications less than after esophagogastrostomy the operation is not the final answer to the problem of esophageal achalasia Partial gastrectomy pyloroplasty or gastroenterostomy should be seriously considered in patients with postoperative regurgitation Pyloroplasty can be done routinely at the time of esophagocardiomyotomy in an effort to relieve gastroesophageal regurgitation

[Although the Heller operation is now generally recommended for the surgical treatment of cardiospasm few articles have appeared giving data on the success of the operation The complications of esophagitis and hemorrhage which have made anastomotic procedures unpopular apparently can also attend the Heller operation although to a lesser degree Any operative procedure on the gastroesophageal junction unfortunately may facilitate gastroesophageal reflux as well as aboral flow Such reflux is particularly damaging in cardiospasm since esophageal peristalsis in this disease is permanently impaired and cannot evacuate any gastric contents that may regurgitate into the esophagus when the patient is lying down —*Ed*]

STOMACH AND DUODENUM

Clinical Value of Gastrointestinal Cytologic Diagnosis Cyrus E Rubin Barbara W Massey Joseph B Kirsner Walter L Palmer and David D Stonecypher[5] (Univ of Chicago) report results in about 300 patients whose gastrointestinal tract was examined cytologically Presence of benign or

(5) G t oe t logy 25 119 138 Oct ber 1953

malignant disease was established by histologic examination or clinical observation in 216 cases

Digestive tract cytologic study requires meticulous preparation of the patient and skilful use of cell collection methods Since this study if correctly done compares favorably with radiology and endoscopy the expenditure of energy is justified If the patient gargles for 15 minutes with a 1% solution of benadryl® or pyribenzamine® discomfort during passage of the tube is minimized An injection of 130 mg sodium phenobarbital may also be given Intubation is accomplished through the mouth instead of the nose to avoid confusion by collection of nasal epithelium Oily material should not be used to lubricate the tube because it prevents adherence of cells to the slides To prevent contamination the patient is encouraged to expectorate saliva and blow his nose as necessary during the procedure Not more than 10 15 minutes should elapse between aspiration and fixation of cells During collection the aspirate should be placed in an ice bath to prevent enzymatic digestion

Collection of cells from the esophagus is the simplest of the digestive tract procedures All nine proved squamous cell carcinomas of the esophagus were diagnosed correctly by cytologic study

Several methods have been developed for collection of gastric cells A simple rapid technic that regularly yields an abundance of well preserved cells remains to be developed The authors have found use of the antral abrasive balloon followed by chymotrypsin lavage satisfactory Of the 111 proved gastric lesions 66 of the 69 benign and 35 of the 42 malignant lesions were predicted correctly by cytologic findings The initial x ray diagnosis was correct in 41 of the benign and 33 of the malignant cases there were 10 false positive and 18 indeterminate x ray reports With cytologic study there were only three false positive diagnoses With all methods including endoscopy and clinical study 109 of the 111 cases were correctly diagnosed

Four of eight carcinomas of the pancreas and one lymphosarcoma of the duodenum were diagnosed cytologically X ray changes were present in only two of the pancreatic cases Experience with hepatic and biliary malignancy was too limited for conclusions

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Clinical Value of Gastrointestinal Cytologic Diagnosis Cyrus E Rubin Barbara W Massey Joseph B Kirsner Walter L Palmer and David D Stonecypher[5] (Univ of Chicago) report results in about 300 patients whose gastrointestinal tract was examined cytologically Presence of benign or

(5) G st oente logy 25 119 138 October 1953

muscularis mucosae is responsible for the gastroscopic appearance Contraction of the muscularis mucosae may cause tissue fluid shifts at the mucosal surface and lead to the appearance of dulness and decreased translucency

[The lack of correlation among gastroscopic appearance histopathologic findings and clinical symptoms indicates that gastroscopically diagnosed hypertrophic gastritis cannot be regarded as an established clinical entity —Ed]

Pain in Chronic Gastric Ulcer Basic Anatomy and Mechanism are discussed by V J Kinsella[7] (Sydney Australia) who demonstrated histologically two main groups of nerves in chronic gastric ulcer The nerves of the edge (sides) of the ulcer are divided ends of the submucous and myogastric plexuses They are deeply embedded within inflamed and infiltrated but still well defined anatomic layers and are usually covered by thickened mucosa and submucosa They are akin to end bulbs found in amputation stumps The nerves of the gap (floor of the ulcer) are either completely absent or are undergoing progressive destruction within the inflammatory *layers at the ulcer base Since their destruction is complete* before the ulcer reaches them they are separated from gastric acid by the three innermost inflammatory layers of Askanazy and by the blood circulating in the granulation layer The protection afforded by these layers is evidenced by the finding of intact leukocytes and in one case undigested meat fibers in the ulcer base Both groups of nerves are therefore beyond the reach of gastric juice and direct irritation by acid is not the cause of ulcer pain

The cause of ulcer pain is found in the inflammatory reaction around the ulcer The many nerves of the edge lie in close association with blood vessels and pain fluctuations during the day are brought about by alterations in volume pressure and velocity of blood flow with altering tissue tension in the inflamed area In addition relaxation of gastroduodenal postural tone accounts for pain relief after the taking of food or alkali Exacerbations during the year are due to acute flare ups of chronic inflammation Inflammatory processes such as antral gastritis and duodenitis may cause ulcer like pain even in the absence of ulceration When ulcer is present pain originates in the palpable lesion throughout the full thickness of the ulcer Motor activity may cause pain secondarily by

(7) La t 2 353 361 A g 22 1953

For examination of the colon a 1 L Ringer s solution enema is given slowly Distribution is promoted by varying *the patient s position* and massaging the abdomen After 10 minutes the return is collected by gravity drainage and massage and the residuum evacuated Ten drops of ovalbumin/100 cc solution is added before centrifugation Twenty seven of 33 proved colonic malignancies were diagnosed preoperatively by cytologic study 18 had been diagnosed by initial x ray examination 10 were not seen and 4 reports were indefinite With all methods correct diagnosis was made in 31 of the 33 cases

In the entire series the lesions were found initially in most instances by x ray study or endoscopy Cytologic study differentiated benign from malignant lesions in 91% of cases Of the proved benign lesions 98% were correctly diagnosed by cytologic study and 66% by initial x ray findings All methods combined gave a 100% accuracy Of the proved malignant lesions 81% were diagnosed correctly by cytologic study and 66% by the initial x ray study All methods combined gave a 94% accuracy

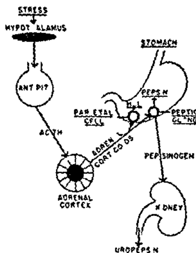
Chronic Hypertrophic Gastritis II Histopathologic Significance **Eddy D Palmer**[6] (Walter Reed Gen l Hosp) states that there is poor correlation between accepted gastroscopic interpretation and histopathologic findings in gastritis Chronic hypertrophic gastritis was diagnosed 190 times during 2 500 gastroscopic examinations Gastric biopsy specimens were taken by vacuum tube technic from mucosal areas diagnosed gastroscopically as chronic hypertrophic gastritis 53 times from 43 stomachs There were only 11 abnormal specimens *In none was the disease more than relative and mild and* no glandular hyperplasia foveolar hyperplasia or excessive infiltrative disease was found

The gastroscopic appearance of chronic hypertrophic gastritis is distinctive and characteristic However it is not dependent on histopathologic disease Round cell infiltration of the interstitial tissue does not indicate a diagnosis of chronic hypertrophic gastritis Epithelial disease is the sine qua non for diagnosis The gastroscopic finding of pebbling indicates merely some infrequent physiologic state of the areae gastricae It is possible that an abnormal tonic quality of the

(6) Ga t oe t ology 26 496 50 M h 1954

units/24 hours a 168% increase In subjects without gastric disease corticotropin compound F compound B or cortisone produced a mean uropepsin excretion of 12 530 units/24 hours Increased excretion was noted on the first or second day of administration and reached a peak in four or five days Physical stress such as surgery or coronary pain in patients without ulcers was associated with a uropepsin excretion of 8 000 57 000 units/24 hours

In three vagotomized patients with duodenal ulcer acid



F g 73 — Ho m nal pathw y b wh ch m nd sed g t id d pep (Cou y f G y S J t l G t oe t l gy 5 156) Octobe 1953)

pepsin and uropepsin response to corticotropin was the same as in patients with intact vagi The mean uropepsin excretion in stressed vagotomized patients was 24 000 units/24 hours compared with 22 000 units in patients without vagotomy Patients with subtotal gastrectomy responded to stress and corticotropin similarly to patients whose vagi and antrums were intact if adequate gastric mucosa was present Atropine 2 4 mg and banthine* 150 300 mg daily did not alter uropepsin response to the hormones in normal subjects or ulcer patients

Surgical procedures such as vagotomy induced sufficient

squeezing this tender area of tissue Acid, if strong enough may increase motor activity and is therefore a tertiary cause of pain

The hypothesis that acid acting on nerve endings in the floor of the ulcer is the primary cause of ulcer pain is based on unnatural experiments false anatomy and faulty pathology

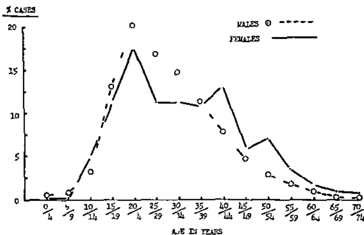
[Dr Kinsella an outstanding student of pain mechanisms comes out of the corner fast lets go with a flurry of left jabs delivered straight from microscopic anatomy uses the rules of physics to sink a brace of rights to the body swings several mean physiologic uppercuts and ends up with a one two three of clinical observations to the head The end of the round finds the proponents of the acid hypothesis of peptic ulcer pain groggy and on the ropes but the next round will surely find them again pushing the fight In the heat of battle Dr Kinsella does not hesitate to use some of the tactics for which he berates his opponents and his stimulating argument is sometimes weakened by unconvincing analogy by assertions backed by no more than the word obvious and by the assumption that a description of nerve function can be read on a microscopic slide —Ed]

Significance of Hormonal Factors in Pathogenesis of Peptic Ulcer Seymour J Gray Colin Ramsey Robert W Reifenstein and John A Benson[8] (Boston) believe that emotional and physical stress may cause increased gastric acid and pepsin secretion by a hormonal pathway through the pituitary adrenal axis independent of the vagus nerve or gastric antrum Previous studies indicate that adrenal steroids stimulate gastric secretion of acid and pepsin and may cause epigastric pain reactivation perforation or hemorrhage of pre existing ulcer or new ulcer formation (Fig 73) Ulcer pain may be induced in both vagotomized and unvagotomized patients The recurrence of pain parallels the rise in pepsin and uropepsin coincident with maximal adrenal stimulation However pain begins four or five days before maximal acid response is reached

Uropepsin excretion in the urine closely reflects the peptic activity of the stomach and represents fairly constantly about 1% of the gastric pepsin secretion When stimulated with corticotropin or cortisone gastric juice pepsin increased an average of 186% whereas uropepsin increased 161% in unvagotomized patients The mean normal uropepsin excretion of 100 patients without gastric disease was 2 350 units/24 hours whereas 215 patients with peptic ulcer excreted 6 775

(8) Ga t oe t ology 25 156-172 O tobe 1953

ulcer symptoms The peak incidences of onset of ulcer symptoms are in early adulthood and again about the time of the menopause (Fig 74) If onset of ulcer symptoms is related to 5 year periods centered on the actual menopause or the expected menopause taken as age 45 the greatest incidence will be found in the period 2½ years before and after the menopause If complications of ulcer are handled in the same manner the number of complications occurring in the five year



F g 74 —Ag t n et f ympt m f pept l m l (1 393) d f m l (400) (Cou t y f Cl k D H B t M J 1 1 54 1 57 J 6 1953)

period centered on the menopause is more than double that of any earlier or later period

Active Duodenal Ulcer in Pregnancy was observed by J Alfred Rider Joseph B Kirsner and Walter L Palmer[1] in 3 of 3 849 women delivered in one year at Chicago Lying in Hospital This suggests that active peptic ulcer during gestation may not be as rare as has been assumed

One patient had had a diagnosis of duodenal ulcer nine years earlier Remissions and exacerbations had occurred but ulcer distress had not been present during three previous pregnancies In the eighth month of the last pregnancy she had symptoms and roentgen evidence of a duodenal crater

(1) G t oe t l gy 24 357 361 J ly 1953

stress and adrenal response to produce a fall in circulating eosinophils with a gradual return to preoperative levels In three patients average uropepsin excretion was increased from 5 000 units/24 hours to 52 000 on the third to fourth post operative day and back to preoperative levels in five to seven days the same time the eosinophils returned to normal Patients with brain tumors involving the hypothalamus excreted 7 770 13 580 units of uropepsin/24 hours

Uropepsin excretion is increased in patients with Cushing s disease and greatly reduced in those with hypopituitarism and Addison s disease

Cortisone compound F compound B and corticotropin were the only steroid or pituitary hormones capable of affecting gastric secretion The fact that uropepsin excretion does not reach a maximum until 4 5 days of corticotropin stimulation and that gastric juice requires 7 14 days more is further evidence of pure hormonal stimulation since vagal stimulation *induces a more rapid response The significant influence* of hormones on gastric secretion may explain recurrence of ulcers in patients successfully vagotomized

[The increased acid secretion induced by adrenal steroid develops slowly over days and in this respect does not resemble the more rapid secretory stimulation effected by histamine and hypoglycemia This difference deserves consideration as it emphasizes the superficial character of the analogy made between Dr Gray s findings in man and the report that increased gastric acidity occurs in monkeys within three hours of giving corticotropin or stimulating the posterior pituitary (Porter *et al* Surgery 33 875 1953)

The next two articles provide further evidence of the influence of the endocrines on the course of peptic ulcer although it is apparent that pregnancy cannot be counted on to give complete protection against this disease —Ed]

Peptic Ulcer in Women D H Clark[9] (Glasgow) studied 330 women with duodenal and 70 with gastric ulcers in an attempt to determine the effects of menstruation pregnancy and the menopause on the course of peptic ulcer Menstruation had little effect on ulcer symptoms whereas pregnancy had a definite beneficial effect During 140 of 313 pregnancies (118 women) the patients were free from symptoms and during 136 they were improved Thus it would appear that in almost 90% of ulcer patients symptoms are in abeyance during pregnancy Early postpartum return of symptoms was common

The menopause appears to have a detrimental effect on

(9) B r M J 1 1 5415 J 6 1953

brings system of variants which includes capacity (potentiality of intellectual development) stability (variation from warm sympathetic realistic heavy to coldish abstract elegant) validity (variation from timid cautious tense to alert self reliant free) and solidity (variation from impulsive easily carried off subjective to steady circumspect and objective) The duodenal ulcer patients in each series were more often supercapable superstable subvalid and subsolid compared with controls The gastric ulcer patients were no different from the controls Duodenal ulcer patients classified as subvalid showed the following traits more often than controls meticulous pedantic indecisive ambivalent insecure anxious slightly compulsive shy self conscious nervous irritable rushed easily fatigued and restless Duodenal ulcer patients often had a combination of increased intellectual capacity and a relative lack of energy which implies discrepancy between a striving to maintain activity on a high level and a restricted power to do so i e a source of chronic conflict If this conflict is accentuated it may be accompanied by autonomic disturbances in the upper digestive tract with the formation of chronic peptic ulcer

Only stability could be correlated with body build The substable persons were more often wide heavy and superstables (i e interests directed inward indifferent abstract) were tall narrow This supported the belief that the different degrees of stability reflect an essential constitutional property of the individual The duodenal ulcer patients from the psychiatric clinic had an asthenic type of neurosis more often than their controls a diagnosis of oligophrenic or endogenous depression was fairly rare The degree of stability was an important factor in prognosis In the superstables the disease was more often found to have a serious course even when compared with substables of similar type of body build In superstables the disease appeared earlier and the course was independent of age at the onset of ulcer symptoms The frequency of peptic ulcer in close relatives of superstable duodenal ulcer patients was probably greater than in relatives of substable duodenal ulcer subjects The frequency of peptic ulcer was higher among close relatives of healthy superstable persons than among such relatives of other healthy subjects Therefore superstability is not secondary to the ulcer disease

In the second patient the ulcer also antedated the pregnancy but remissions and exacerbations continued throughout gestation The third patient had no previous history of ulcer but severe ulcer distress with hematemesis developed in the last trimester The recurrence of ulcer in one patient and development of ulcer in another during the last trimester is in accord with previous observations and presumably is related to the increased gastric secretion observed late in pregnancy

The precise incidence of active ulcer during pregnancy is not known although evidence suggests that it is lower than in nonpregnant females Gastrointestinal x ray studies of pregnant women with digestive symptoms would undoubtedly increase the recognition of ulcer

[For medicolegal reasons however radiologists caution against any but the most essential radiologic studies in the first half of pregnancy In experimental animals radiation can produce fetal anomalies —Ed]

The Peptic Ulcer Individual Study in Heredity, Physique and Personality Gerdt Wretmark[2] (Orebro, Sweden) studied 130 duodenal and 34 gastric ulcer patients 169 nonulcer controls comparable in all other respects to the ulcer group, 90 patients with duodenal and 32 with gastric ulcer who had some type of neurosis (selected from a psychiatric clinic) 128 nonulcer controls of comparable age from the same clinic and 520 other persons of age comparable to the first series and used mainly to estimate the frequency of peptic ulcer in the age groups under consideration All patients and controls were men

Peptic ulcer occurred more often among brothers of peptic ulcer patients than could be expected on the basis of a survey of the population the ratio between the number of ulcer cases found and the number expected being 1 9 1 Patients with duodenal ulcer statistically showed a preponderance of vertical over horizontal growth as compared with controls of the same age i e they more often had tall narrow body build The gastric ulcer patients did not show a similar statistically significant tendency These findings indicate that constitutional and hereditary factors are important in peptic ulcer formation The prognosis of duodenal ulcer in persons who are tall narrow is less favorable than in those of wide heavy body build

The patients personalities were judged according to Sjo-

( ) A t ps h t et neu l sc d v pp 84 1953

pouch dogs produces as much as a sevenfold increase in secretion of gastric juice from isolated fundic pouches (Fig 75) No such increase occurs after vagotomy when the antrum has been resected previously from the main stomach of the Heidenhain preparation or a gastroenterostomy had been done Resection of the fundus and corpus of the main stomach also increases the secretion of the Heidenhain pouch 390%

Tentative explanations for these phenomena include the hypothesis that an acid environment inhibits function of the antrum Following either division of the vagi or fundusectomy acidity in the main stomach decreases Since there is less acid antral function is less inhibited the gastric phase of secretion is potentiated and the isolated pouch responds with increased secretory activity Gastroenterostomy may counteract this stimulation of the gastric phase of secretion by allowing food to by pass the antrum

[Studies such as these underlie the hypothesis that the antrum may act like a thermostat when the gastric contents approach neutrality the antrum is stimulated to elaborate it secretory hormone when the contents are highly acid gastrin release is inhibited. According to th s hypothesis antral mucosa left in place in a B llroth II operation would favor formation of stomal ulcer becau e the residual ant al mucosa is constantly exposed to alkal ne duodenal contents In the type of segmental gastric resection described in the next article however leaving part f the antrum n place should do no harm because it is exposed to such acid as is secreted in the upper portion of the stomach —Ed]

Evaluation of Segmental Gastric Resection for Treatment of Peptic Ulcer Lloyd D MacLean Warren Hamilton and Thomas O Murphy[4] (Univ of Minnesota) compared the results of this operation in 90 patients with those achieved with the Billroth II type gastric resection in 953 patients Segmental gastric resection is designed to remove 90 95% of the acid secreting area of the stomach but not the pyloric antrum thus avoiding the difficulty encountered in closing the duodenal stump Weight of resected specimens in segmental gastric resection and in the three quarter gastric resection Billroth II type in nonobstructed duodenal ulcers differed little indicating comparable degrees of resect on To avoid pyloric obstruction following segmental resectio longitudinal pyloromy with transverse closure was performed Two operative deaths occurred giving a mortality rate of 2 2%

Preoperatively average free gastric acid with triple his

(4) Su g y 34 227 237 A gu t 1955

The observations justify the conclusion that an inherited predisposition for duodenal ulcer exists and that superstability is an essential factor in this predisposition

About two thirds of the duodenal ulcer patients could be divided into two widely different prognostic groups The course of the disease was favorable in 44% of the patients who were substable and of wide heavy body build it was favorable in only 9% of the group of superstables of tall narrow body build

[As the author writes the value of this work may to a great extent be ascribed to the availability of control material Because control material is both available and used with scrupulous statistical care this article is unusual in the annals of psychosomatic studies on peptic ulcer In addition Dr Wretmark is enough of a psychiatrist to realize that disciples are not won by esoteric jargon although psychiatric terms are used they are always explained in ordinary English as well Only one fault can be found the study was not blind in the sense that the author apparently knew which patients had ulcer at the time of the interview Otherwise his observations are most convincing —Ed]

Stimulating Effect of Vagotomy on Gastric Secretion in Heidenhain Pouch Dogs Shirl O Evans Jr Jose M Zubiran Jack D McCarthy Herzl Ragins Edward R Woodward and Lester R Dragstedt[3] (Univ of Chicago) demonstrated that severing the vagus nerves to the main stomach of Heidenhain

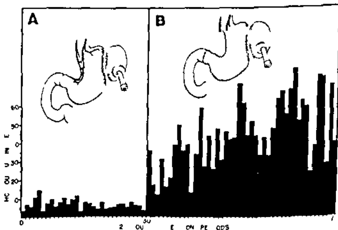


Fig 75 —Q nt tat e effect f v got my on g t c sec t H d nhai ch dog A g ch w th g i tact t ma n t m h B g d t d. (Courtesy f E a s S O J et al Am. J Physiol 174 19 2 5 A g t 1953)

(3) Am J Physiol 174 219 2 5 A g t 1953

8 Gm magnesium trisilicate with 50 ml of the phenol red solution

It has long been taught that ingestion of alkalis particularly the soluble ones leads to a rebound secretion of gastric juice Introduction of alkalis as of any substance probably stimulates gastric secretion but if secretion is neutralized by alkali still present it is not harmful nor did it affect the experiment which was to determine whether there was rebound secretion which might be deleterious after the alkali had left the stomach

No evidence of a rebound secretion of acid within 2½ hours of introduction of alkali and dye into the stomach was found In eight patients the highest concentration of acid found in any of the five fractional samples was less than the initial reading In the other eight it was higher but in only two was it greater by more than 20 mEq /L In view of the normal variation in fasting secretion these differences are not significant

[If as suggested in the articles immediately preceding this one the antral phase of secretion is stimulated by alkaline gastric contents a rebound secretion of gastric juice following the introduction of alkalis might be expected Failure to observe such a rebound does not however disprove an antral response to changes in pH particularly since it is difficult to analy e separately the several factors that determine the composition of human gastric juice —Ed]

Prognosis in Gastric Ulcer Treated Conservatively Benjamin M Banks and Louis Zetzel[6] (Harvard Med School) studied the clinical course and late results of medical management of gastric ulcer in 48 patients treated initially in an urban hospital These cases represent a comparatively small portion of all cases reviewed but in view of rigid criteria for their selection the findings may have increased significance Four patients were followed more than 15 years 7 for 10 15 years 20 for 5 10 years and the others for an average of 2½ years A typical ulcer sequence of pain with relief by food or antacids was present in 34 and massive internal bleeding occurred in 17

Three fifths of the patients received optimal management in terms of length of hospitalization amount of rest regulation of diet appropriate medications laboratory and x ray studies In the remaining cases there was a tendency to discharge the patient before healing was fully established For

(6) New England J Med 249 1008-1013 J 11 1953

tamine stimulation was 88 degrees in duodenal ulcer patients and 50 degrees in gastric ulcer patients Postoperatively only five patients had free acid following triple histamine stimulation and the highest value was 30 degrees Early postprandial distress was absent in 54% of the Billroth II resection patients and 49% of the segmental resection group Symptoms were mild in 26% moderate in 17% and severe in 3% of the Billroth II group mild in 37% and moderate in 14% of the segmental resection group Hypoglycemic symptoms occurred in only five of the segmental resection group and in 17% of patients having Billroth II resections Intolerance or distaste for foods such as milk ice cream and sweets was noted in 50% in this series and was as common as in other forms of resection In the segmental gastric resection group weight loss was common and most striking in the first year or two Postoperative anemia occurred in only one patient In the 10 36 month follow up period there were no recurrences

A slower gastric emptying time was seen after segmental gastric resection than after a Billroth II resection Overall evaluation showed results were excellent in 25% satisfactory in 66% and poor in 9% of the segmental resection group whereas they were excellent in 26% satisfactory in 63% and poor in 11% of the Billroth resection group

It is unnecessary to remove a duodenal ulcer to cure it Leaving the antrum attached to the residual stomach is not hazardous even though clinical trial suggests that a procedure which excludes the antrum from the stomach potentially will cause peptic ulcer recurrence

Effect of Alkalis on Fasting Human Stomach J S Staffurth (St Thomas s Hosp London) studied 11 patients with duodenal ulcer 2 with prepyloric ulcer and 3 with abdominal pain of other cause After aspiration of gastric contents through a narrow bore tube alkalis were introduced into the fasting stomach with a nonabsorbable dye and gastric secretion observed by taking 5 cc samples at half hour intervals for 2½ hours The experiment was not prolonged further because by this time a meal is normally taken especially by patients who are prescribed alkalis Half the patients were given 8 Gm sodium bicarbonate and 50 ml of a solution containing 40 mg phenol red/100 ml The other half received

(5) La c t 2 227 9 A g 1 1953

recurrent pain and hematemesis Early in the course of his disease the ulcer had been cauterized at operation Repeated x ray examinations always disclosed an active ulcer in the cardia At a second operation 13 years later carcinoma of the stomach was discovered

The hypothesis that recurrent gastric ulcer is more prone to malignant change than the original ulcer remains to be proved A correlation between incidence of malignant degeneration and frequency of recurrences would be suggestive but not conclusive evidence A policy of resection for any recurrence because of fear of malignancy implies that all patients with gastric ulcer should be operated on as soon as the original diagnosis is made Since recurrences may be expected in 50 90% of cases during a five year follow up it seems logical to perform the operation promptly and thus to protect the patient from an almost inevitable double jeopardy of cancer Unless one is prepared to adopt such a policy it is preferable to consider each recurrence on its merits and to reserve surgery for cases that have recurred under good medical management fail to heal promptly or present serious complications

The patient with a gastric ulcer should be hospitalized immediately for evaluation and decision concerning the method of therapy indicated The sine qua non for continuation of conservative medical treatment in the hospital is progressive diminution in size of the gastric ulcer on serial radiologic examination and the indispensable prerequisite for discharge of the patient is the complete disappearance of the lesion with return of normal pliability of the gastric wall in that area

Chronic Gastric Ulcer Comparison between Gastroscopically Controlled Series Treated Medically and Series Treated by Surgery B F Swynnerton and N C Tanner[7] report on 387 men and 111 women with chronic gastric ulcer treated at St James s Hospital London during 1940-46 One series (262) was treated medically and the other (254) surgically with 18 patients appearing in both series Late information concerning nearly all was obtained in 1952 giving a minimum follow up of 5 and a maximum of 12 years Criterion for inclusion in the study was the presence of an active chronic gastric ulcer which in the medical series was seen gastroscopically Pa

(7) Brit M J 2 842 847 Oct. 17 1953

example in many patients radiologic findings in the stomach were not rechecked before discharge

Of the 48 patients only 11 remained free from ulcer symptoms throughout the follow up period 7 remained well after one or more recurrence and 2 patients listed as well died subsequently of unrelated causes Twenty patients continued to have periodic exacerbations of ulcer symptoms six of these eventually had operations Eight died of verified carcinoma of the stomach

Reports from other sources indicate that 13 19 8% of patients operated on for ulcer originally presumed to be benign have a carcinomatous lesion In this series only one of four patients remained symptom free over three years one of six died of carcinoma of the stomach and one of five was operated on or refused operation despite the most urgent indications

Of the 20 patients classified as well 7 had one or more symptomatic recurrences confirmed by x ray within five years In each case the gastric ulcer was in the same location previously reported

Of the eight patients who eventually died of gastric carcinoma all but one were past 50 when first seen Seven gave a classic history of ulcer In all duration of digestive symptoms before initial hospitalization was suggestive of a benign lesion Two patients had symptoms for 2 years the others for 3 5 11 16 18 and 20 years In five the lesion was situated in the upper third of the stomach just below or in the cardia Symptoms subsided within a few days of initiation of treatment in five cases and gradually in two One patient had symptoms intermittently Serial x ray studies in the hospital showed some healing in two complete healing in one and no change in two three were not re examined but all patients had prompt and completely favorable clinical response to treatment

In retrospect only one of the eight met the currently accepted rigid radiologic criteria for complete healing of the lesion In five cases the location of the ulcer in the region of the cardia and its relative inaccessibility to cure except by radical operation probably influenced the decision to carry on with medical measures One patient with a large ulcer in the cardia was treated in hospitals repeatedly during 16 years for

active pulmonary lesions when operated on were still alive after seven and nine years and their lesions were considered inactive In the medical series three men had died of pulmonary tuberculosis the diagnosis for only one was recorded at the time of admission for gastric treatment The evidence concerning an increased risk of pulmonary tuberculosis after gastrectomy is inconclusive

In three fourths of the medical patients symptoms of gastric ulcer recurred despite the fact that the ulcers might be expected to be mild or of recent onset The large number of deaths should by the end of 5 12 years have eliminated most patients who were not operated on initially because of age or infirmity Re examination of the criteria for inclusion of patients in this series does not reveal any obvious factor in the method of selection to account for the appalling results One is forced to conclude that medical treatment though it may heal the ulcer will keep it healed in less than a fourth of the early or milder cases

It might be expected that patients with short histories before diagnosis would respond well to treatment and rarely relapse However in this series their chances of remaining symptom free was still under 50%

No coherent picture emerges from a study of the relationship of dieting and the taking of alkalis to recurrences Some patients diet the whole time some when they have pain and others never The position may be summarized by saying that 75% of those who have had no further recurrences have given up dieting whereas 61 4% of those with frequent recurrences have adhered to a diet the whole time Nearly all patients whether they have had recurrences or not try to avoid certain foodstuffs

Of every 10 patients in the surgical series still alive the result has been satisfactory in 8 moderately successful in 1 and poor in 1 A small late operative morbidity must be taken into account when judging late operative results Despite careful investigation of many patients postoperatively the authors have been unable to find any case of proved stomal or gastric ulcer following gastrectomy for gastric ulcer In several iron deficiency anemia has responded well to iron Although some patients lost weight no gross vitamin deficiencies have been noted

tients with additional duodenal ulcers or scars were not included The ulcer histories of 28% of the patients included the occurrence of manifest bleeding with more than one episode in 16%

Data on duration of symptoms indicated that there is a tendency for men with short histories to be treated medically Why this is not true for women is not clear It may be that women if they do not have an operation early become adapted to the presence of ulcer better than men possibly because they can for domestic reasons treat recurrences more thoroughly The operation rates decrease for men with a history of over 20 years They too have learned to live with their ulcer For this reason their appearance at a hospital should excite suspicion that recent symptoms which they attribute to ulcer may be due to other causes

The impression that the high posterior aspect of the lesser curve is the site of predilection for chronic gastric ulcers in women was confirmed There was a pronounced drop in frequency as the lower portion of the stomach was approached and ulcers in the pyloric antrum and canal were exceptional In men the distribution of ulcers from the cardia to the pylorus was more even with the highest incidence in the mid and lower body and over 10% distal to the angulus The reason for the differences between men and women is unknown

Surgical mortality for partial gastrectomies was 6 3% Sixty one medical and 56 surgical patients have died since their initial stay in the hospital Despite the fact that the medical series might be expected to contain the majority of the aged and infirm patients the death rates in the two series are almost the same

Cancer had developed in 15 medical and 11 surgical patients In 10 (6 and 4 respectively) the primary growth was probably in the stomach

Pulvertaft has suggested that the incidence of pulmonary tuberculosis may increase after gastric resection of peptic ulcer Follow up on 233 patients in the surgical series showed that 6 men had died of this disease—1 seven months 3 three years 1 five years and the other eight years after operation at ages ranging from 49 to 63 In none was the diagnosis recorded at the time of operation but two patients who had

were 71 deaths among the medically treated patients originally diagnosed as having benign ulcer 1 7% died of malignant ulcer as contrasted with 4 85% in cases of benign ulcer in which resection was done

This study indicates that a month or less of intensive medical management in many cases of gastric ulcer is justified The responsibility for differentiating benign and malignant ulcers is great and requires the utmost vigilance but the responsibility should be borne by the gastroenterologist in the interest of avoiding unnecessary surgery and of maintaining unimpaired digestive physiology

[Two of these articles as well as the article by Cain *et al* in the 1953 54 YEAR BOOK page 540 indicate that about three of every four patients with gastric ulcer suffer recurrences On the other hand clinical results in three of four gastric ulcers followed by the Lahey Clinic group were rated as good In spite of this discrepancy fairly uniform impressions may be gained from these articles (1) Medical treatment of gastric ulcer is justified in many cases (2) The results of surgery are very satisfactory in 80% of cases but the mortality of operation is still far from negligible (3) A recurrent ulcer may be considered a strong indication for operation not necessarily because of the fear of malignancy but because the recurrence in itself is evidence that the ulcer is intractable to medical management (4) The most serious medical mistake is discharge of a patient with gastric ulcer without radiologic evidence that the ulcer has disappeared completely

The figures dealing with the incidence of malignant ulcers are interesting In one series 8 of 48 patients treated medically for gastric ulcer eventually died of cancer of the stomach In the English series gastric cancer developed in only 6 of 262 patients treated medically and interestingly enough appeared in 4 of ?54 patients treated surgically In the Lahey Clinic series of 4?? patients treated medically only 7 eventually died of cancer of the stomach, but 30 additional patients with malignant gastric ulcers were maintained on medical management for longer than one month —Ed]

Pyloric Channel Ulcer According to Butsch these ulcers present no characteristic clinical features Eusterman however indicated that in most cases they give rise to the syndrome pylorique consisting of a short stormy course with intermittent pyloric obstruction and painful spasm of the pylorus Roentgen diagnosis although often difficult has been considered more accurate than any other diagnostic procedures including exploratory laparotomy E Clinton Texter Jr George J Baylin Julian M Ruffin and Clarence W Legerton Jr[9] (Duke Univ) studied 55 patients to determine if a recognizable clinical picture exists

Three characteristic variations from the usual clinical pic

(9) G t oent r l gy 4 319 3 7 July 1953

Only a fourth of the patients in the medical series compared with over three fourths in the surgical series have had no further trouble despite the probability that the medical series contained most patients whose ulcers were initially considered to be mild or of short duration

Problem of Gastric Ulcer Reviewed Study of 1 000 Cases Frances H Smith Russell S Boles Jr and Sara M Jordan[8] (Lahey Clinic) report data on 912 patients with benign and 88 with malignant gastric ulcer Ages ranged from 10 to 89 Males predominated—70% in the benign and 73% in the malignant group Surgery was done on 497 with benign ulcer suspected malignancy being the indication in over half and on 81 with malignant ulcer There was no significant difference in weight loss in those with benign or malignant ulcers

Pathologic examination revealed that 22 6% of benign and 28 1% of malignant ulcers were in the prepyloric region Roentgenograms showed duodenal deformities in 19 7% of patients with benign and 20 2% with malignant ulcer This suggests that demonstration of this deformity is not helpful for differential diagnosis

Recurrence was the indication for surgery in 16 3% of patients with benign and 18 5% with malignant lesions Follow up on 380 with benign lesions treated with resection showed that 78 7% had good 14 2% fair and 7 1% poor results Of 397 with benign lesions treated medically 75 1% had good 13 8% fair and 11 1% poor results The follow up periods varied from 2 months to 29 years but the results in those followed for long or short periods did not differ appreciably There was little difference in morbidity between the surgically and medically treated benign ulcer groups

Over all incidence of malignant ulcers in the total series was 8 8% but it was 16% in those with recurrent ulcers Of 474 patients with benign ulcer who underwent gastric resection 23 died in the postoperative period of 23 who had other operative procedures 6 died Of 60 with malignant ulcer who underwent gastric resection 2 died postoperatively and of 21 who had other operative procedures 6 died After the postoperative period 44 with benign ulcer and 20 with malignant ulcer died Of the latter 18 died of carcinoma of the stomach and 2 of pulmonary embolism after other surgery There

(8) J A M A 153 1505 1505 Dec 26 1953

may be missed on x ray study and yet be found by the pathol ogist

Forty two re examinations were done on 38 patients who had had duodenal ulcers In six symptoms were worse the crater was larger in four of these and unchanged in two In eight symptoms were unchanged the crater was larger in two unchanged in five and smaller in one Of 28 whose symptoms were less or had disappeared 1 had a larger crater in 6 crater size was unchanged and in 21 it was smaller Re exami nations (55) were performed on 50 patients with cap deformity alone In one patient whose symptoms were worse the duo denal deformity was unchanged In 16 whose symptoms were unchanged the duodenal deformity was unchanged Of 38 patients whose symptoms were less or had disappeared the duodenal deformity was worse in 2 unchanged in 35 and less in 1

In most instances the ulcer crater became smaller as the symptoms subsided but it was often present though there was complete remission of symptoms Duodenal cap deformity seldom changed despite changes in symptoms While symp toms are present re examination by a barium meal is unnec essary and after symptoms have disappeared radiologic assessment of treatment is usually of no value

The radiologic method of demonstrating duodenal ulcer craters is far from foolproof and failure to show a crater in the presence of symptoms cannot be taken as an indication of healing The radiologist can help the clinician if the original diagnosis is in doubt X rays may be of prognostic value to show whether the crater is getting smaller but they will not indicate how long it will remain There is no indication for x ray study in a known sufferer from duodenal ulceration while symptoms remain or when symptoms recur after a period of freedom from pain and the films are available for inspection

[More observatio s like this a e needed In many stud es recommend i g th o that t eatment for peptic ulcer heal ng time in terms of radiologic d sappearance of the ulcer crater is offered as one of the criteria used in judging the recommended treatment Up to now however no one has bothered to study the valid ty of this criterion. In all probabil ty rad olog c evaluation of disappea ance of ulcer craters is a rather crude estimate of ulcer healing particula ly since techn cal difficulties are many and tl e va iations between individual radiologists great —Ed]

ture of peptic ulcer were observed Nausea and vomiting uncommon in uncomplicated peptic ulcer were the most frequent complaints being present in 78% of the patients Vomiting tended to occur in periodic episodes 30 minutes to 2 hours after meals Atypical abdominal pain which lacked the usual pain—food—relief cycle was present in 71% of the patients Pain was unrelieved by eating in 36% and was initiated by eating in 29% Colicky pain occurred frequently after eating and was relieved only by vomiting or by narcotics It appeared to be due to dysynergia of the pylorus When normal gastric evacuation resumed pain ceased Constant pain lasting days to weeks and similar to that of carcinoma of the stomach or pancreas or of chronic pancreatitis was also prominent Significant weight loss suggestive of neoplasm was noted in over half the patients

Only 20% of the patients presented the clinical picture considered typical of peptic ulcer and in most cases the diagnosis was made only after roentgen study In four patients with surgically proved channel ulcer pyloric obstruction was the only roentgen finding Twenty six of the 55 patients required surgical treatment

Value of Radiology in Assessing Progress of Duodenal Ulceration under Treatment George Simon and George du Boulay[1] (St Bartholomew s Hosp London) were unable to find any critical studies in the literature on the usefulness of radiography to demon trate healing of a duodenal ulcer although many authors believe that x ray re examination is valuable especially when an ulcer crater has been previously demonstrated Examination of 134 patients with duodenal ulcer showed 63 with definite craters and 71 with duodenal cap deformity alone Many of these were re examined by barium swallowed at intervals of a few weeks and two years during which they had been treated medically

Only 6 of the 63 patients with ulcer craters had definite evidence of persistence of the crater at the second or subsequent examination Ulcer craters were found in only 12 of 17 patients on whom gastrectomy was done A depression lined with mucosa may look like a crater on the x ray and yet be normal to the pathologist whereas an ulcer in a deformed cap

(1) Proc R y Soc Med 46 655 662 August 1953

groups in which periodic symptoms had continued The natural course of peptic ulcer appears to be the main factor which determines whether the patient will persevere with treatment

The relapse rate was over 50% during the first 12 month test period and nearly 70% after 5 years This indicates that the natural history of peptic ulcer and the recurrence rate are unaffected by a 12 month period of medical after care under almost ideal conditions As far as useful military service is concerned a stable personality and a desire to remain well were more important than medical care regular living and diet

[The facts presented in this article cast serious doubts on the thesis that the natural course of peptic ulcer can be altered by manipulating the patient s environment and living habits —Ed]

Prolonged Drug Therapy in Peptic Ulcer I Evaluation of Banthine® as Adjunct to Conventional Ulcer Therapy was undertaken concurrently in seven cities by E C Texter Jr C W Legerton Jr Julian Ruffin J S Atwater David Cayer F D Cheney R A Jackson B G Oren and J M Rumball [3] The study was designed to show whether the addition of banthine® in ulcer therapy improved the long term course if recurrences were fewer or less severe if complications were less frequent and if surgery could be avoided

Presence of an ulcer was proved by x ray in all patients They received a bland diet with six feedings a day and antacids Half the patients were given 100 mg banthine® four times a day and half of them 0 4 mg atropine sulfate four times a day Satisfactory data were obtained on 250 patients over a mean observation period of 13 months (6 24 months) 131 took banthine® and 119 atropine (table) Eleven discontinued therapy due to side effects

In the banthine group ® 24 5% had no recurrences during treatment compared to 10 1% in the atropine group From comparisons of recurrences during treatment in mild moderate and severe cases it was evident that mild cases responded much better to banthine® than to atropine and moderate cases slightly better to banthine ® in severe cases there was little difference in response

The total number of complications was the same in both groups Hematemesis or melena occurred in eight banthine®

(3) South M J 46 1061 1069 November 1953

Effect of Diet and Regular Living Conditions on Natural History of Peptic Ulcer James W Rae and R S Allison observed 63 Royal Navy men with proved peptic ulcers for over 12 months All were living as a corporate unit with their own mess arrangements and were under the care of a medical officer A suitable diet at regular times and snacks between meals were provided and all could have a special light diet for a few days without hospitalization if symptoms recurred Employment was provided according to each man s training and experience Casual and makeshift work was not allowed and no overtime or physically difficult work was done Complications of perforation hematemesis or melena and pyloric stenosis had previously occurred in 55 5%

At the end of the 12 months nearly half the men had lost no time from work because of dyspepsia and about a quarter had been off work for a week or less The diet and regular living conditions appeared valuable in preventing incapacitating symptoms and serious relapses although the men s work capacity was less than normal Clinically the patients could be divided into three groups (1) 48 subjects with typical recurring attacks of epigastric gnawing pain relieved by food and alkalis (2) 11 with continuous atypical dyspepsia and other ill defined symptoms and (3) 4 with no symptoms until a complication threatened Dietary indiscretions defective teeth irregularity of meals and the use of tobacco and alcohol did not seem to be important causes of relapses or failure of the ulcers to heal However symptoms sometimes recurred after a leave or interruption of regular routine Men in group 2 lost the greatest time and required the most individual attention

A five year follow up study of 52 patients revealed that only 4 had no symptoms 42 (81%) had been subject to recurrent symptoms which were severe enough to cause the men to be off work at some time 32 (62%) lost more than one week of work every year and 10 (19%) lost more than three weeks per year Over two fifths of the patients followed a fairly regular regimen of diet and alkaline powders one fifth had given up all forms of treatment and two fifths took alkalis and followed a suitable diet only when symptoms recurred Most of the men who followed a fairly regular regimen were in the

(2) Q rt J M d 419 455 October 1953

of mucus together with the low columnar and cuboidal cells lining the crypts of the gastric gland The viscous mucus contains conjugated glycoproteins and has specialized capacities of adhesiveness cohesiveness viscosity adsorbtiveness power and acid neutralization The cellular layer of the mucous barrier not only serves to replace mucus as it is removed from the surface but on penetration of the mucus by an irritative agent interposes a solid shelf of tissue between the mucus and the more delicate gland tubules The cement substance is loosened locally and the prompt desquamation of surface epithelial cells releases a mucus of especially high viscosity and tenacity to reinforce the outer layer of secretion The loss of tissue is soon compensated by rapid reconstitution of the disrupted cell layer

The mucous barrier is effective chiefly against HCl and pepsin in the gastric contents Gastric secretion and the two component mucous barrier that prevents peptic ulcers are in equilibrium The mucous layer permits movement of gastric juice from the lumen to gastric tissue or from gastric tissue to the lumen and by its self regenerative capacity repairs any defects

Peptic ulceration results from a shift in the dynamic balance between the gastric secretion and the mucous barrier The secretion of mucus by the columnar cells may be deficient for metabolic or other reasons Local physiologic change may slow regeneration after impairment of the mucous epithelial layer Among factors predisposing to such changes are local ischemia of emotional origin with corollary localized anoxia inadequate supply of nutritive elements and local accumulation of metabolic waste material the nutritional state of the body endocrine factors and neurotrophic influences of organic and emotional origin

The pathogenesis of peptic ulcer should be studied in the light of the two component self regenerating mucous barrier that normally protects the mucosa from aggression by its own gastric juice as well as from exogenous traumatic agents

[Control of gastric acidity has b en consid red the cornerstone of medical treatment of pept c ulcer for 50 years but the limitations of this t eatment are becom g increasi gly apparent and are a cause of dis satisfaction to those physicians whose goal is curing the patient of his ulcer disease rather than merely closing the mucosal defect existing at the moment. Because of this dissatisfact on new approaches to ulcer therapy a e constantly being sought Dr Hollander in his own words

treated and five atropine treated patients perforation occurred in one banthine® treated and four atropine treated patients Four patients in both groups had progressive pyloric stenosis requiring surgery Of 20 patients requiring surgery 12 were taking atropine and 8 banthine ®

Ulcer patients fared significantly better on conventional therapy supplemented with banthine® than with atropine The beneficial effect was inversely proportional to the estimated severity of the ulcer Most of the patients improved regardless of the drug taken It is likely that diet and supervision

FINAL RESULTS OF BANTHINE® AND ATROPINE TREATMENT FOR PEPTIC ULCER

RESULTS	BANTHINE ®	ATROPINE
Symptom free	25	12
Markedly improved	37	25
Moderately improved	37	31
	99 (75 5%)	68 (57 2%)
Slightly improved	7	12
Unchanged	22	16
Worse	3	23
	32 (24 5%)	51 (42 8%)

played a role Improvement does not necessarily indicate healing of an ulcer Persistence of ulcer craters and failure to decrease hemorrhage perforation or the need for surgery suggest that banthine® does not alter the eventual course Greatest benefit is achieved when banthine® is used as an adjunct to conventional therapy

[Among the multiple claims made for the assorted anticholinergics now on the market this article is outstanding for its objective and sound evaluation of banthine® in comparison to atropine After reading this report a clinician should know exactly what he can and cannot expect from banthine® Since the effects of all the anticholinergics now available are similar to those of banthine® some agents being slightly more and many considerably less potent the usefulness of banthine® in the treatment of peptic ulcer may be taken as representative of the usefulness of all the newer anticholinergic drugs —Ed.]

Two component Mucous Barrier Its Activity in Protecting the Gastroduodenal Mucosa against Peptic Ulceration. Franklin Hollander[4] (Mount Sinai Hosp New York City) states that self digestion of the stomach is prevented by the gastric mucous barrier composed of (1) the viscous sheet of mucus covering the inner wall of the gastric cavity and (2) the layer of tall columnar cells immediately beneath this sheet

(4) A M A Arch Int Med 93 107 1 0 Jan 1954

It is possible that had it been given for a longer period beneficial effects might have occurred

Most peptic ulcer patients can be treated by a month of modified bed rest in a hospital with bathroom freedom and two to three hours of ambulation daily Magnesium trisilicate can be taken whenever the patient has pain or discomfort After discharge from the hospital the patient continues the *same regime at home for three weeks and is then encouraged* to return to work The important factors in any therapeutic regime for peptic ulceration are mental and/or physical relaxation to assist the natural tendency for remissions to occur

Histiotherapy of Gastroduodenal Ulcer Many foreign tissues both animal and vegetable when implanted or injected into the body produce substances known as biologic stimulants which promote cellular metabolism and quicken the vital processes of the host Experimentation with histiotherapy has been extended to many fields since the early work of the Russian ophthalmologist Filatov and opinions concerning its efficacy vary widely T A Pinos Marsell and Jose Garcia Galera[6] (Barcelona) used this treatment for patients with gastroduodenal ulcer in whom prolonged bed rest suitable diet and all available therapeutic measures had failed The six subjects included patients with gastric duodenal and stomal ulcers

METHOD—Placental tissue is prepared for use by keeping it under refrigeration at a temperature of 0 4 C for at least one week after which it is cut into small cubes The cubes contained in Petri vessels are placed in a 70 C oven On removal they are put into sterile flasks and autoclaved at 120 C Tissue prepared by this method used by Gate Vachon and co workers has the disadvantage of possessing only limited keeping qualities To avoid this the tissue may be desiccated and rehydrated at the time of use Desiccated tissue is prepared by refrigerating the placenta at 2-4 C for 10 days washing it carefully and cutting it into disks 1 cm in diameter and 3 mm thick The di ks in a Petri ampule are then put into a vacuum oven at 70 C for 1 hour followed by 12 hours at 40 C with moisture absorbents (sulfuric acid calcium chloride) They are then autoclaved at 120 C

When amniotic implants are desired the tissue is kept at 4 C in a 3% solution of sodium salicylate After seven days it is cut into 4 cm cubes and autoclaved for an hour at 120 C Extracts are prepared by crushing the placenta screening it under aseptic conditions and keeping it for six days at 4 C in a penicillin streptomycin

(6) R p 6 enf m p d g t 32 35 365 J ly A g 1953

presents a concept which affords a basis for experimental investigation of the ulcer problem drastically different from the older hypothesis founded or grounded primarily on augmented and prolonged gastric secretion by the ulcer patient Others pursue the will-o the wisp of ulcer cure in different directions Robaden is the latest of the so called mucosa protecting substances that have been tried in the treatment of ulcer and up to now found wanting (following article) A peek at an approach apparently used behind the Iron Curtain is afforded via the Spanish article on the histiotherapy of gastroduodenal ulcer (p 495) On the face of it the use of much buffeted placental tissue for treating peptic ulcer would seem to possess little rationale but recent newspaper accounts tell of placental extracts being used even in the U S A for the treatment of arthritis Finally as the article on thoracoscopic vagosympathectomy (p 496) indicates the surgeon is also searching for a quick and snappy ulcer cure —Ed]

Value of Strict Dieting, Drugs and Robaden in Peptic Ulceration The possibility that peptic ulcer patients may lack a mucosa protecting substance prompted the development of robaden which is a protein free extract obtained from the stomach and small intestine of freshly slaughtered young animals The water soluble part of the extract is used by injection and the insoluble part is taken orally in tablet form P R C Evans[5] treated 111 patients with peptic ulceration including 27 with gastric ulcer of whom 3 also had a duodenal ulcer and 87 with duodenal ulcer Four different plans were used (1) strict gastric diet strict bed rest and sedatives antispasmodics and antacids (2) the same with the addition of robaden (3) post ulcer diet and daily ambulation of about two hours and (4) the same with the addition of robaden *Patients on robaden were given each morning for 21 days* 1 ml of the appropriate injection intramuscularly with 1 tablet three times a day before meals for 7 weeks then 1 tablet daily for the first 10 days in each month for 3 months If pain persisted more than a few days after hospitalization the daily injection of robaden was increased to 2 ml for a week Patients not on robaden were given placebo injection and tablets on the same schedule *All patients were followed* for at least six months after discharge from the hospital

In both the gastric and duodenal ulcer groups rest in hospital and a light diet gave as good results as those achieved by rest in hospital and a strict diet plus antispasmodics and antacids There was no evidence that robaden improved the results However the patients only received it for five months

(5) B r M J 1 612 616 Ma 13 1954

spect to gastric resection and removal of the ulcer It was performed in 50 patients with duodenal ulcer After a two year follow up 47 patients were free from symptoms and roentgenograms showed no ulcers in 44 In one patient no roentgenogram was obtained and in two others bulbar deformities were seen Three patients had subsequent gastric resection in other hospitals though in these cases an additional left sided vagotomy and sympathectomy may have helped as it did in six patients not included in this series

In combined vagotomy sympathectomy the patient was usually hospitalized for two days In a few instances the procedure was done with the patient ambulatory Patients were not restricted in dietary smoking drinking or working habits

[The completeness and permanence of nerve section carried out by this approach is open to question In addition motility studies in four patients subjected to simultaneous bilateral sympathectomy and vagectomy showed a clearcut vagectomy effect (J A M A 146 1406 1951) —Ed]

LIVER BILIARY TRACT AND PANCREAS

Separation of Serum Pigments Giving Direct and Indirect van den Bergh Reaction P G Cole and G H Lathe[8] (London) extracted bile pigments from the serums of patients with hemolytic jaundice hepatitis and obstructive jaundice By reverse phase chromatography these pigments were separated into two types The fast moving pigment is more soluble in water and gives the direct van den Bergh reaction The slow moving pigment is more soluble in organic solvents and gives the indirect van den Bergh reaction

Autopsy bile contains considerable amounts of fast moving direct reacting pigment smaller amounts of indirect reacting pigment and several other unidentified pigments One of these appears to be biliverdin A green pigment can also be separated at times from the plasma of patients with long standing biliary obstruction but this does not appear to be biliverdin

The direct and indirect reacting yellow bile pigments when prepared by chromatography contain no protein From this and other evidence it is concluded that the nature of the van den Bergh reaction does not depend on the splitting by

(8) J Cl P th 6 99 104 M 1953

solution It is then centrifuged and the superficial layer is put into 5 cc ampules which are sterilized at 55 C and stored under refrigeration

Tolerance for the implants was perfect, and the procedure may be considered innocuous when carried out under aseptic conditions The principal benefits derived from treatment were relief from pain weight gain and psychic improvement The results apparent on radiologic examination however were disappointing persistence of the ulcer niche was common In only one case did improvement in the patient s condition justify discharge

Right Thoracoscopic Vagosympathectomy in Duodenal Ulcer Report on First 50 Patients after Two Year Follow Up is presented by E Kux and A Batschwaroff[7] (Univ of Innsbruck) One disadvantage of vagotomy in the treatment of duodenal ulcers is the development of pylorospasm which subsides only after several weeks On the other hand sympathectomy always results in an open pylorus even if there was pylorospasm before surgery This was noted in 400 patients who had thoracoscopic sympathectomy However sympathectomy alone was not as successful as vagotomy because with the former ulcers of long standing did not respond at all in 14% of patients and recurred in 12%

Based on these observations the authors tried to counteract pylorospasm and gastric atony following vagotomy by a sympathectomy In a two stage procedure right sided vagotomy was performed through a thoracoscope and at the same time the splanchnic nerve was blocked with procaine The pylorus opened leaving the patient asymptomatic During the weeks following the first stage the side effects of vagotomy —vomiting gastric dilatation and pylorospasm—developed In the second stage right sided splanchnic sympathectomy was performed again by thoracoscopy and the symptoms subsided promptly The procaine effect of several days duration was due to its sympathicolytic and not to its anesthetic action

Right sided vagotomy may be performed without disadvantage if sympathectomy is carried out at the same time thus severing the secretory motor sensory and vasoconstrictor pathways This procedure corresponds in functional re-

(7) Tho k ru g 1 377 38 No mber 1953

difficult to interpret this test for bile in the urine is highly satisfactory as both a sensitive and a simple procedure —Ed]

Observations on Outbreak of Infectious Hepatitis in Baltimore during 1951 are reported by Abraham M Lilienfeld Irwin D J Bross and Philip E Sartwell[1] who uncovered cases occurring in a housing project by means of a house to house survey Information was obtained from 792 households (3 790 individuals) in the 888 inhabited dwellings By the time of the survey visit 101 cases with jaundice had occurred Exclusion of other causes of jaundice was made on clinical

ANNUAL ATTACK RATES OF CASES OF INFECTIOUS HEPATITIS WITH JAUNDICE BY AGE AND SEX 1951

Age Group Y	Males		Females		Both Sexes
	Population	Rate %	Population	Rate %	Rate %
0 4	370	1 4	3_8	0 9	1 1
5 9	381	4 5	383	7 1	5 8
10 14	290	4 5	315	8 3	6 4
15 19	157	0 6	177	4 0	2 4
20 +	578	0 1	811	0 1	0 1
Total	1 7/6	2 3	2 014	3 4	2 9

grounds and appropriate laboratory tests In all 109 cases with jaundice (69 in females) were found giving a total annual attack rate of 2 9% (table) The cases were mild and occurred sporadically in the early part of the year There was an increase in incidence during June followed by a decline during the summer then an increase to a maximum in September and October

Secondary attack rates were computed all cases occurring in a household during a two month period after the first or primary case being considered secondary For patients not receiving gamma globulin the secondary attack rate was 8 8% In other civilian outbreaks in this country secondary attack rates have ranged from 20 to 40% In a London outbreak the rate was 7 4% In England the secondary attack rates are in general higher in rural (20 30%) than in urban outbreaks All previous studies in the United States were on rural outbreaks This difference in urban and rural areas may represent a higher endemic level of infection in urban areas with the likelihood that there will be fewer susceptible individuals in case of a focal outbreak One of 74 persons given

(1) Am J P b H 1h 43 1085 1096 S pt mb 1953

alcohol of a linkage with protein nor on the presence of inhibiting or catalyzing substances but on the existence of two types of pigment The indirect reacting pigment is probably bilirubin the nature of the direct reacting material has not yet been established

[At present both the biochemical identity and the physiologic significance of the two types of bilirubin that can be separated into direct and indirect reacting on the basis of the van den Bergh reaction are completely unknown If the results reported here are confirmed current opinions concerning bilirubin metabolism must be extensively revised —Ed]

Simple Test for Urine Bilirubin, based on the coupling of bilirubin under specific conditions with a stable diazonium compound p nitrobenzene diazonium p toluene sulfonate (bilazo) is described by Alfred H Free and Helen M Free[9] (Elkhart Ind) Bilirubin is adsorbed from urine on a 19 × 19 × 2 mm mat composed half of asbestos and half of cellulose fibers The bilirubin is concentrated on a small area of the mat s surface For convenience the diazonium compound is incorporated in a tablet which is placed on the mat and moistened When bilazo comes in contact with the adsorbed bilirubin a blue or purple color results

PROCEDURE —Five drops of urine is placed on the mat and 1 tablet of bilazo is placed on the moistened area Two drops of water is allowed to flow over the tablet and onto the mat Color is read after 30 seconds The amount of bilirubin is proportionate to the speed of the color development and its intensity Color on the tablet and any color appearing on the mat after 30 seconds are ignored

By dilution it is possible to estimate the bilirubin in urine containing large concentrations of the pigment The urine is diluted until a faint positive reaction is obtained This is about 0 05 mg /100 ml The original concentration can be calculated

At bilirubin concentrations of 0 1 mg /100 ml trained and untrained observers can routinely record positive results Trained operators can identify as little as 0 05 mg /100 ml The sensitivity is high but not so high that false positive results occur with normal urine The minimal equipment required makes it possible to do this test anywhere with accuracy The technic is rapid one test can be done in less than a minute and several dozen in an hour

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(9) Gastroenterology 24 414 421 July 1953

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(9) G stroent ology 24 414-421 J ly 1953

Evidence has accumulated that infectious hepatitis in childhood is not necessarily benign Chronic hepatitis ascites and cirrhosis have been reported However the condition appears to be more benign in children than in adults and complete prevention of the disease in childhood may be unwise Gamma globulin is definitely indicated for sick children exposed to hepatitis especially if debilitated by chronic digestive and nutritional disturbances

Because of potential shortage of gamma globulin the smallest effective dose should be used Studies in progress suggest that 0 01 cc /lb is highly effective

[The two preceding articles indicate what type of person is apt to get infectious hepatitis und r what condition hepatitis is apt to spread *and how it can be prevented More recent studies have confirmed the fact* that a dose of gamma globulin of 0 01 cc /lb is effective in preventing r attenuating infect ous hepatitis —Ed]

Carrier State in Viral Hepatitis Joseph Stokes Jr J Edward Berk Leonard L Malamut Miles E Drake Jeremiah A Barondess Winslow J Bashe Irving J Wolman John D Farquhar (Philadelphia) B Bevan R J Drummond and W d A Maycock (London) R B Capps and A M Bennett[3] (Chicago) describe the detection by circumstantial evidence and by direct evidence in volunteers of three persons who carried hepatitis virus B (serum) in their blood and of two who carried hepatitis virus A (infectious) in the feces The blood borne viruses appeared to have been present for at least 5½ 3 and 1 years and the hepatitis virus A was present in the stools for indeterminate periods The three carriers of hepatitis virus B had no history of jaundice and no symptoms However two had positive results of liver function tests one of whom had evidence of liver damage on biopsy One patient was apparently a silent carrier for at least three years and transmitted the virus transplacentally to an offspring

The first patient with hepatitis virus B had donated blood to 18 persons in 4 of whom hepatitis developed (in 3 within 41-43 days after transfusion) Results of liver function tests on the carrier were positive and were not improved by chlortetracycline therapy *The patient s blood was injected parenterally* into four volunteers hepatitis and jaundice developed in one and questionable hepatitis in another Oral administra

(3) J A M A 154 1059 1065 M 27 1954

gamma globulin had infectious hepatitis two days after receiving the injection—a secondary attack rate of 1.4%.

The disease appeared to spread by the fecal-oral route from a focus near the center of the project in a radial fashion similar to that often seen in measles and poliomyelitis. The rate of spread appeared slower than in these diseases but this may merely represent a longer incubation period.

In institutional outbreaks it is feasible to administer gamma globulin to all inmates. This is impossible in civilian life. However, it would be possible to give gamma globulin to households in close proximity to one already affected.

Family Outbreaks of Infectious Hepatitis: Prophylactic Use of Gamma Globulin. Benjy F. Brooks, David Yi-Yung Hsia and Sydney S. Gellis (Children's Med. Center, Boston)

INCIDENCE OF HEPATITIS INFECTION AMONG EXPOSED ADULTS AND CHILDREN IN FAMILIES TREATED WITH GAMMA GLOBULIN AND THOSE NOT TREATED

Group	Untreated		Treated	
	No. Exposed	No. with Hepatitis	No. Exposed	No. with Hepatitis
Over age 15	63	0	33	1* (3%)
Under age 15	51	18 (35%)	22	0
Totals	114	18 (16%)	55	1 (2%)

*Hepatitis developed two days after gamma globulin administration.

observed 64 patients with hepatitis in 46 families. Gamma globulin was given to all immediate members of 17 families but none to the other 29 families, which served as controls. The recommended dose was 0.1 cc./lb. body weight with a maximum of 5 cc. in infants and children and 10 cc. in adults. A few persons received 0.01-0.06 cc./lb. Additional cases of hepatitis developed in 48% of the untreated families but in only one person among the family contacts treated with the material. Jaundice became manifest in this patient only two days after gamma globulin was given (table).

It is obvious that the exposure of children to hepatitis within family groups results in a surprisingly high incidence of the disease. Gamma globulin is extremely effective in preventing the disease. It must be given early and at least five to seven days before onset of jaundice to be effective. Adults involved in these outbreaks have a relatively high degree of immunity.

(2) New England J. Med. 249:58-61, July 9, 1953.

of the hepatitis a mortality of 11% these two cases had the shortest incubation periods (54 and 55 days)

Volunteers received subcutaneous injections of 1 000 units of the suspect thrombin in 1 or 2 cc solution In almost 50% hepatitis with jaundice developed another 20% had hepatitis without jaundice This confirms the pre ence of the agent of homologous serum hepatitis in the samples of thrombin tested and proves the etiology of the epidemic at Maine General Hospital The occurrence in neurosurgical patients indicates the extent to which thrombin is used in such operations as compared to general surgery

The widespread use of thrombin is evidence of its useful ness in surgical procedures In the light of past experience the value of blood fractions whose safety had not been demon strated must be weighed against the risk of homologous serum hepatitis Commercial preparations containing human fluids or blood products must be considered potential sources of infection until proved otherwise The only human blood frac tions that have not been shown to transmit homologous serum hepatitis are gamma globulin albumin and antihemophilic globulin as prepared by ethyl alcohol precipitation

Serum Hepatitis from Pooled Irradiated Dried Plasma William P Murphy Jr and William G Workman[5] (Nat l Inst of Health) investigated the records of 464 patients who had received pooled dried irradiated human plasma 150 or more days previously Whether or not human blood products other than plasma or blood were used was not determined The records of 180 patients receiving 403 units of plasma were adequate to warrant study of the occurrence of serum hepatitis as a result of the plasma transfusion Of the 180 23 (12 8%) had signs and symptoms of serum hepatitis Of 64 patients who had received only plasma no whole blood 6 (9 3%) had hepatitis A 12 8% incidence of hepatitis is sig nificantly higher than that of hepatitis due to blood trans fusion alone (0 5%) or of infectious hepatitis (0 02%) The findings indicate that the methods used for irradiation of pooled plasma in large scale production are not wholly effec tive in destroying the agent of homologous serum jaundice

Serum Hepatitis Apparently Acquired from Irradiated Plasma Robert M Albrecht Robert F Korns William G

(5) J A M A 15 1421 14 3 A g 8 1953

tion of the patient s feces to eight volunteers did not cause hepatitis Parenteral injection of blood from an infant with hepatitis whose mother transmitted the virus transplacentally caused hepatitis and jaundice in one of five volunteers and nonicteric hepatitis in another The mother s blood caused hepatitis and jaundice in 2 and nonicteric hepatitis in 4 of 10 volunteers Parenteral injection of blood from the third carrier of hepatitis virus B into five volunteers caused hepatitis and jaundice in one

Carriers of viral hepatitis A may have the virus in their feces as well as in the blood The two virus A carriers had symptoms but no jaundice and results of liver function tests were mildly positive Oral administration of feces from one carrier caused hepatitis and jaundice in one of four volunteers the same was true of feces from the second carrier The incubation periods were 22 and 26 days in contrast to 33 100 days among the patients with viral hepatitis B Human carriers of chronic active viral hepatitis A explain the outbreaks of the disease and its endemic characteristics in certain areas

The carrier state may develop when the host fails to attain a solid immunity early in infection with one of the viruses Improved methods for control of viral hepatitis B must await development of efficient technics for eliminating or inactivating hepatitis virus B in whole blood or blood products or technics for easy and rapid identification of carriers Until such technics are available elimination of donors with histories of jaundice or abnormal liver function tests or both may help reduce the incidence of the disease

Human Thrombin as Vehicle of Infection in Homologous Serum Hepatitis is discussed by Joseph E Porter Morrill Shapiro and George L Maltby (Maine Gen l Hosp) Miles E Drake Jeremiah A Barondess Winslow J Bashe Jr and Joseph Stokes Jr (Univ of Pennsylvania) and John W Oliphant William C L Diefenbach Roderick Murray and N C Leone[4] (Nat l Inst of Health) At Maine General Hospital homologous serum hepatitis developed in 15 of 48 neurosurgical patients given thrombin during operation None of 27 neurosurgical patients operated on during the same period and not receiving thrombin had hepatitis Two patients died

(4) J A M A 153 17 19 S pt 5 1953

for the last determination before discharge was 113 μg The mean value for the first determination of total serum iron binding capacity was 335 μg /100 cc with a normal mean for men of 311 $\pm$ 28 μg and for women of 309 $\pm$ 27 μg In most patients serum iron binding capacity decreased as the infection subsided As in other infections serum copper levels rose The variation in serum iron and copper occurred independently

There was some correlation between serum iron and total serum iron binding capacity However in two patients serum iron varied independently of serum iron binding capacity Also the increase in the serum iron was greater than the increase in the total serum iron binding capacity It is thus unlikely that increased iron binding capacity can explain the increased serum iron in acute hepatitis

[The increased serum iron content of patients with hepatiti is interesting but of limited diagno tic value s nce the values for serum iron in hepatitis and other causes of jaundice show considerable overlapping —Ed]

Adrenal Hormone Therapy in Viral Hepatitis—*I Effect of ACTH in the acute disease*—To evaluate the role of adrenal hormone therapy Alfred S Evans Helmuth Sprinz and Robert S Nelson[8] (M C U S A) treated 20 patients with corticotropin and 10 with cortisone and compared the course with that of alternate controls not receiving hormones and of 200 patients treated before this study Absolute bed rest with bedside commode privileges and a 4 200 calorie low salt diet were prescribed Ten of the corticotropin group were treated within 10 days of onset of illness and 10 within 10 20 days The control groups were similarly divided Of the cortisone group all were treated within the first 10 days of illness Five patients with severe hepatitis and six in hepatic failure given corticotropin cortisone or both were also studied

The patients given corticotropin within the first 10 days had a slightly longer over all course than the controls whereas those given corticotropin later in the disease had a slightly shorter over all course than the controls In general corticotropin produced a prompt sharp initial fall in total and one minute serum bilirubin values in 18 of the 20 patients After five days of therapy bilirubin level had decreased an average

(8) A I t Med 38 1115 1133 J e 1953

Beadenkopf Melvin B Goodman and Frances B Locke[6] (New York State Dept of Health Albany) studied 131 recipients of irradiated plasma and 131 matched controls from three hospitals to determine the incidence of hepatitis one to six months after plasma administration Ninety one patients in each group received whole blood in addition Ten cases (7 6%) of acute hepatitis occurred in the group receiving plasma and one case (0 8%) among the controls It is believed that the cases in the group receiving plasma can be attributed to the plasma and that irradiation of the plasma lots studied failed to prevent or significantly to reduce the transmission of serum hepatitis

[The demonstration in the preceding four articles that the virus of serum hepatitis may be carried in the blood for long periods of time that all human blood fractions with the exception of three specific products can transmit serum hepatitis and that irradiation by ultraviolet light does not inactivate the virus in icterogenic plasma increases our knowledge of the transmission of serum (virus B) hepatitis and al o emphasizes that methods for its control are still lacking A recent suggestion (J A M A 154 103 1954) that the virus is inactivated by keeping plasma at room temperature for six months requires confirmation —Ed.]

Serum Iron, Total Iron Binding Capacity of Serum and Serum Copper in Acute Hepatitis were measured by P Brendstrup[7] (Copenhagen) in seven men and three women Acute hepatitis is the only infectious disease in which serum iron increases There is no satisfactory explanation for this occurrence One author has attributed it to a decreased deposition of iron and another to decreased excretion in the bile Increased liberation from disintegrating liver cells together with inability of the liver to absorb iron from the physiologic decomposition products of hemoglobin has also been postulated It has been suggested that gastroduodenitis complicating the hepatitis may abolish the physiologic blockade to iron absorption Another theory is that an increase in the total iron binding capacity of the serum could increase the serum iron Hepatitis also differs from other infections in that alpha globulin decreases and beta and gamma globulins increase

The mean value for serum iron in the 10 patients when first tested was 155 μg/100 cc The value for normal men was found to be 125 $\pm$ 25 μg and women 101 $\pm$ 24 μg Plasma iron values fell as recovery progressed and the mean value

(6) J A M A 152 1423 14 6 Aug 8 1953
(7) Acta m d sc di av 146 107 113 1953

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(8) A I t Med 38 1115 1133 J 1953

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(6) J A.M A 15 1423 1426 Aug 8 1953
(7) Acta med scand nav 146 107 113 1953

II Effect of cortisone in the acute disease—Evans Sprinz and Nelson[9] found that normal total serum bilirubin levels were achieved two weeks sooner in patients treated with cortisone than in the controls (Fig 76) This was also true of brom sulfalein retention Cortisone treated patients were ready for discharge 17 days earlier than were the controls No effect on thymol turbidity cephalin cholesterol flocculation alkaline phosphatase or cholesterol esters was noted Cortisone produced an initial drop in levels of gamma and serum globulin and also a secondary rise in those of serum globulin All 10 patients had glycosuria—3 with fasting and 2 with postcibal hyperglycemia Two of the cortisone group relapsed but none of the controls Histologic findings confirmed the clinical and laboratory impressions of more rapid progress to apparent healing among cortisone treated patients than among the controls fat vacuolation was twice as prominent as in corticotropin treated patients and four times as prominent as in the alternate controls (Figs 77 and 78)

III Effect of ACTH and cortisone in severe and fulminant cases—Evans Sprinz and Nelson[1] found in five severe cases of viral hepatitis that hormone therapy caused a prompt initial fall in serum bilirubin level in another bromsulfalein retention persisted Of three who had multiple relapses two recovered and one was left with chronic hepatitis In six cases of fulminant hepatitis with actual or impending coma and liver failure the course was essentially unaltered to death Later two patients in hepatic coma were given large doses of cortisone (1 000 mg daily) One given both cortisone and chlortetracycline died the other given cortisone penicillin and levulose and choline intravenously survived after 48 hours in coma Large doses of cortisone appear to deserve further trial in fulminant hepatitis

Cortisone and corticotropin can decrease jaundice The total duration of apparent illness in patients given cortisone and under certain conditions those given corticotropin has been significantly shortened Cortisone treated patients have tended to more rapid healing evident on clinical laboratory and histologic study These benefits are sharply limited by the 25% relapse rate (usual rate 1%) Other limitations in

(9) A I t M d 39 1134 1147 J 1953
(1) Ibid pp 1148 1159

52% in treated patients and only 20% in untreated controls However, serum bilirubin reached normal simultaneously in both corticotropin and control groups Bromsulfalein retention reached 10% or less slightly later in the corticotropin group who were also ready for hospital discharge later Thymol turbidity cephalin cholesterol flocculation and alkaline phosphatase values were not affected Cholesterol ester levels tended to return to normal more rapidly with corticotropin which definitely decreased both globulin and gamma globulin levels Increased appetite and sense of

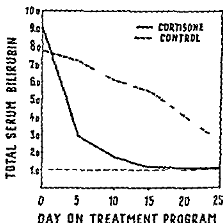


Fig 76—Effect of cortisone on total serum bilirubin in 10 patients as compared to 17 controls (Courtesy of Evans A S et al Ann Int Med 8 1134 1147 June 1953)

well being were prominent The tendency in viral hepatitis to disturbances in carbohydrate metabolism was exaggerated by corticotropin Of the 20 16 patients had glycosuria —7 with fasting and 6 with postcibal hyperglycemia Glycosuria without hyperglycemia was noted in five of the alternate controls Four of the corticotropin patients all treated early in the disease relapsed No relapses occurred in 220 controls Satisfactory progress toward healing was demonstrated by liver aspiration biopsy in both the treated and the control groups However in three of the corticotropin group moderately severe fatty metamorphosis followed therapy a similar degree of change was not seen among the controls

clude side reactions and failure to prevent chronic hepatitis or to reverse fulminant hepatitis Hepatitis is usually benign self limited and accompanied by adequate immunity The high relapse rate after hormone therapy reflecting possible interference with mechanisms important to immunity does not appear to indicate routine use of the hormones

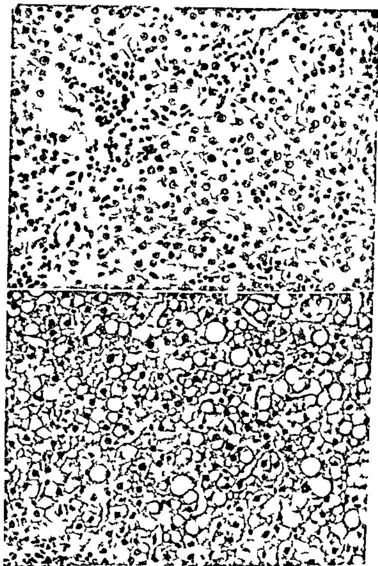
Role of Alcohol in Pathogenesis of Cirrhosis is reviewed by Gerald Klatskin[2] After Laennec's anatomic description of cirrhosis (1826) toxicologists attempted to reproduce cirrhosis in animals by feeding alcohol and possible contaminants of beverages such as phosphorus and copper with failure the theory of a direct toxic action by these agents on the liver was abandoned The current concept maintains that chronic alcohol ingestion leads to or is associated with a specific dietary deficiency High protein diets are believed to correct this deficiency by supplying labile methyl groups in the form of choline and methionine

The validity of this concept is questioned because not all alcoholics with cirrhosis show signs of malnutrition or admit to dietary deficiencies Laennec's cirrhosis is uncommon in malnourished nonalcoholics with chronic debilitating diseases cirrhosis has not been observed in individuals starved or underfed for long periods (prisoners of war) and improvement in cirrhosis has been observed on suboptimal and almost protein free diets This reopens the question whether alcohol may not play a more direct role in the pathogenesis of cirrhosis than by simply reducing dietary intake

Animal experiments suggested that the choline requirement was a function of the caloric intake and that alcohol and isocaloric sucrose supplements increased choline requirements by augmenting caloric intake However redesigned experiments indicated that alcohol and sucrose did increase choline requirements but that alcohol did not necessarily do so by augmenting caloric intake Animals maintained on substantial intakes of alcohol decreased their intake of other foods In man the metabolic effects of alcohol consumption are not completely understood but since alcohol supplies 7 calories/gm it is probable that a heavy drinker greatly reduces the scope of his dietary intake

One must be cautious in transposing results of animal ex

(2) Y J Biol & M 4 2 23 37 September 19 1



Fg 77 (t p) —Li b p y sp c m n taken on 8th d y f ıll bef e cortıso therapy

F g 78 (bottom) —Spec m f m sam p t e t afte 28 d y of ort so ther py o 37th d y f llu , not f t v cuol t

(Co rte y of E ns A S et l A n I t Med 38 1134 1147 J 1953)

all provided the same results The addition of vitamins lipotropic agents and adrenal steroids did not shorten the time required to mobilize the fat Lipotropic agents particularly cyancobalamin parenterally were useful in patients with anorexia or systemic diseases interfering with nutrition

Serial study in 11 patients who continued to eat poorly and consume large quantities of alcohol revealed 1½ 5 years after the initial study portal cirrhosis in 7 fatty liver with beginning fibrosis in 2 and fatty liver in 2 The sequence of fatty liver development of fatty cysts with rupture round cell inflammation and exudation ingrowth of fibrous connective tissue and regeneration of liver cells seemed applicable to the patients in whom cirrhosis developed No objective relationship could be established between rupture of cysts liver cell regeneration or fibrosis Proliferation of reticulum cells fibroplastic metaplasia and serous exudation postulated as responsible for liver fibrosis could not be demonstrated

Since fatty liver is curable it is essential that it be recognized and treated early to prevent development of hepatic fibrosis and its consequences

Cirrhosis of the Liver, according to A K M Abdul Wahed[4] (Dacca Univ) is a common disease in East Pakistan (Fig 79) In a 30 bed ward there will invariably be at least 2 or 3 cases and often as many as 10 Nonobstructive hypertrophic biliary cirrhosis is not common and accounts for not more than 5% of all cases of cirrhosis

Alcoholism is not an etiologic factor in Pakistan because religious precepts forbid the use of alcohol Spices have been considered a factor However the people generally do not overindulge in them and although certain spices such as chili are used in excess by a section of the population cirrhosis is no more prevalent here than among the general population In view of the liver damage produced in experimental animals by diets deficient in methionine and cystine dietary deficiency must be considered an etiologic factor

Long continued administration of methionine and cystine did not improve the clinical features of cirrhosis Vitamin B_1 improved the general condition anemia was reduced and the interval between paracenteses was lengthened The liver itself

(4) J N t M A 45 389 394 N mbe 1953

periments to the problems of Laennec s cirrhosis Even in animals the diet must be at least marginal in lipotropic factors (choline or methionine) before alcohol effects become apparent Animals on a high protein diet show none of the effects of alcohol exhibited by animals on a low protein diet In animals alcohol probably has two effects a nonspecific calorogenic effect leading to reduced food intake and another relating to the mechanism of hepatic fat transport The latter is readily abolished by lipotropic agents

Clinical Observations on Fatty Liver were made by Carroll M Leevy Myra R Zinke Thomas J White and Angelo M Gnassi[3] (Jersey City N J Med Center) in 102 patients in whom *fatty metamorphosis without fibrosis was revealed* by liver aspiration biopsy The most severe fatty liver occurred when the diet consisted principally of carbohydrate and few foods containing lipotropic substances There was no correlation with the amount type or duration of alcohol intake 41 patients drank moderately 17 consumed large quantities of alcohol daily but had periodic remissions and 28 had severe chronic alcoholism Those with heavy alcohol intake and who ate only carbohydrate foods had the severest fatty changes Clinical abnormalities were roughly proportional to the degree of liver fat and disappeared with its mobilization Hepatomegaly present in 86 was the commonest sign Degree of jaundice was frequently unrelated to the amount of liver fat Splenomegaly was not accompanied by additional signs of portal hypertension Ascites and edema were usually proportional to the amount of liver fat though several malnourished patients with little fat had peripheral edema and ascites There was no correlation between the amount of liver fat and liver function tests Patients with chronic alcoholism and fatty liver had findings similar to those with normal histology or focal infiltration After elimination of the fat biochemical abnormalities occasionally persisted

Pilot studies showed that bed rest and a diet adequate in protein and lipotropic substances could transform a severe fatty liver to normal in six weeks *Intracellular fat was mobilized* in three weeks elimination of extracellular fat required four to six weeks A general hospital diet and high carbohydrate high protein diet with either high or low fat content

(3) A M A A h Int M d 9 5 7541 O t be 1953

material has been negative and the stools positive for ova in a few cases Fatty infiltration is a constant finding but even when it is pronounced fibrosis is minimal Steatosis and fibrosis were found constantly in liver biopsy material from 50 patients with malnutrition Except for the local tissue reaction the steatosis and fibrosis in schistosomiasis differ little from these changes in malnutrition

The number of patients examined was limited but it seems probable that the fibrosis seen in advanced schistosomiasis is due to both local tissue reaction about the ova and to steatosis and its sequelae Liver enlargement in such cases may therefore have a dual origin parasitic infection and steatosis

[The common denominator in the pathogenesis of fatty liver and cirrhosis is as shown by the preceding four articles dietary deficiency The deficiency of the protective factors does not appear absolute but relative to the total caloric intake With respect to human cirrhosis specific dietary factors such as methionine cystine and choline which have been shown to protect the rat liver do not appear by themselves to have a clearcut therapeutic effect It is also not yet settled whether fatty infiltration in man is a direct precursor and cause of cirrhosis or whether it appears concomitantly with cellular inflammation and necrosis perhaps the real antecedents of cirrhosis —Ed]

Hepatitis and Cirrhosis of Liver are discussed by a panel composed of William J Eisenmenger Gerald Klatskin Arthur J Patek Jr and Mary Ann Payne with Franklin M Hanger[6] as moderator Patek believes that bed rest is indicated in hepatitis so long as there are clinical signs of acute inflammation or so long as results of liver function tests fluctuate After these results are stabilized one is often confronted by a long period of convalescence during which bed rest is not feasible When treating patients with cirrhosis who require months or years to recover a regimen which has a reasonable chance of acceptance should be prescribed

Klatskin states that once the patient with acute hepatitis feels well and has no jaundice or hepatic enlargement or tenderness and bromsulfalein retention is 10% or less ambulation should be allowed He usually checks the bilirubin and bromsulfalein retention twice during the first week the patient is up If either has increased or the liver is enlarged the patient is returned to bed Some patients seem to have chronically elevated bilirubin levels and bromsulfalein retention

(6) B ll N w Y k A d M d 30 43 65 J ry 1954



F g 79—Pat ts w th cirrhosis of l er i cl d g some w th sple c em a. (Court y f Abd l W hed A K M J N t M A 45 389 394 N embe 1953)

showed no clinical change On cessation of vitamin B_{12} therapy patients lapsed into their former state

In countries where alcoholism is not a factor the cause of cirrhosis is unclear In the presence of dietary deficiencies repeated attacks of malaria dysentery and other infections may lead to cirrhosis

Liver Changes in Schistosomiasis in Children Preliminary Report Eugene Stransky and Naida E Pesigan[5] report on seven cases seen at Philippine General Hospital Liver punch biopsies were used to study the course of hepatic schistosome infection

It has been stated that bilharziasis causes a so called parasitic cirrhosis if the parasite settles in the liver Although there is no doubt that at autopsies on patients with Schistosoma japonicum infections diffuse fibrosis of the liver may be found it is questionable whether it is secondary to the parasitic infection alone or to malnutrition with the marked prolonged fatty infiltration which invariably precedes nutritional diffuse hepatic cirrhosis

Early in schistosomiasis the liver is usually unaffected but in the more advanced stages ova are present In one case repeated stool examinations were negative for ova but ova were found in the liver biopsy tissue Conversely biopsy

(5) J T op M d 56 261 266 No mber 1953

hepatic coma However patients with hepatic insufficiency are highly susceptible to intestinal tract infections and blood stream invasion and administration of chlortetracycline is indicated as a temporary measure Eisenmenger has found that methyltestosterone provides fairly dramatic relief from itching in patients with prolonged severe jaundice and pruritus The relief is such that some patients refuse to discontinue use of the drug In one of these patients the methyltestosterone increased the jaundice Hanger states that although he does not consider this drug cytotoxic one continues to see patients on methyltestosterone in whom intrahepatic inspissation *of bile plugs the center of the lobule Eisenmenger re*ports that use of corticotropin in certain patients with cirrhosis has been complicated by changes in blood coagulation time and development of thromboses Estrogens can be used when indicated in patients with liver disease according to Payne Many women profit by treatment of the menopause even though they have spiders liver palms and other supposed stigmas of high estrogen levels Eisenmenger finds that in case of hemorrhage nothing adequately replaces the use of blood Plasma substitutes such as dextran are inadequate because they disappear rapidly from the blood stream into the urine and ascitic fluid

[It is noteworthy that each of the experts on this panel on the basis of wide clinical experience emphasizes the importance of adequate bed rest in the treatment of hepatitis although the necessity of such treatment is difficult to establish by statistical study of groups of patients managed by different regimens Bed rest, often strict bed rest appears indicated for the occasional patient who has a relapse as he becomes more active —Ed]

Experimental Study of Ascites Posthepatic Venous Stenoses and Transposition of Liver into Thorax P Mallet Guy G Devic J Feroldi and P Desjacques[7] (Lyon) present evidence to support the theory that so called mechanical ascites does not result from portal hypertension but is caused by hepatic venous congestion Hepatic congestion was produced in 32 dogs by partial occlusion of the inferior vena cava in its thoracic segment or by ligation of the suprahepatic veins In addition the liver or a portion of it was transposed into the right thoracic cavity If ascites resulted from hepatic transudation as suggested by Volwiler Grindlay and Bollman it would be expected to appear above the diaphragm while

(7) L on h 49 153 17 F b M 1954

yet when put on mild activity promptly have normal or minimally elevated values

With regard to whether acute hepatitis is ever converted into so called chronic hepatitis by excessive physical activity Payne states that if a persistently tender liver recurrent anorexia and malaise can be considered signs of chronic hepatitis she can cite many cases in which this has happened After an epidemic of hepatitis among the Navajo Indians the percentage of large livers spiders and abnormal liver function tests was greater among children with mild clinical disease who were allowed up than in children with a more severe initial episode and adequate bed rest The only major variable was the degree of activity

Regarding diet in acute hepatitis Payne believes that it should be adequate and well balanced Patek does not consider the evidence sufficient to show that choline or methionine provides additional benefit in liver disease over that of a good diet containing at least 70 100 Gm protein a day The forcing of large amounts of vitamins may possibly do harm For example large doses of vitamin A have been shown to cause liver damage

Eisenmenger states that salt should be restricted only in patients with liver disease who are incapable for one reason or another of getting rid of salt in the urine Sodium ion exchange resins are practically ineffective in a patient with cirrhosis and a strong tendency to form ascites Also some of the ammonium resins release excessive amounts of ammonium ion which perhaps contributed to the development of hepatic coma Constipation is frequent when resins are used and occasionally intestinal obstruction develops For many years it was thought that intravenous administration of human albumin would correct the low serum albumin in cirrhosis and reduce ascites with consequent diuresis It has proved effective only in patients who are relatively easy to control by other methods Aside from its ineffectiveness intensive albumin therapy may initiate hematemesis as a result of a rapidly expanded blood volume

Patek is of the opinion that in general patients with liver disease tolerate sulfonamides quite well although some observers believe that they are harmful to the liver Hanger does not believe antibiotics have a specific curative effect in

hypertension must include esophagoscopy for accurate judgment of the method

Transient Esophageal Varices in Hepatic Cirrhosis, a hitherto unreported phenomenon is discussed by Hugh D Bennett Clifford Lorentzen and Lyle A Baker[9] (V A Hosp Hines Ill) who noted spontaneous disappearance of esophageal varices in 12 of 502 patients with hepatosplenomegaly and abnormal liver function tests Of the total group 419 had cirrhosis 370 of the Laennec s variety 83 had hepatosplenomegaly and abnormal liver function without cirrhosis Incidence of varices in patients with cirrhosis was 26% The 12 with transient varices had cirrhosis or were in a precirrhotic phase The entire group underwent a total of 800 barium studies and 1 000 esophagoscopies

The first five patients had esophageal varices which disappeared without any intervention other than medical therapy In Case 1 hepatomegaly regressed but the varices had disappeared before reduction of organ size In Case 2 there was questionable decrease in liver size Biopsy had shown prominent fatty infiltration Liver dysfunction was mild from the onset In Case 3 no change in liver disease other than disappearance of the varices was noted Melena occurred later but varices could not be demonstrated at that time In Case 4 bleeding was due to uncertain cause varices disappeared without other evidence of change in hepatic status In Case 5 there was bleeding apparently from a single esophageal varix which disappeared after abstinence from alcohol Silent varices can only be discovered by routine barium study and esophagoscopy of patients with cirrhosis In Cases 6 and 7 esophagitis and mediastinitis preceded the disappearance of previously demonstrated varices

In the other five patients with varices normal pressures were found in the portal system at time of laparotomy Splenectomy was performed in four Later esophageal varices could not be demonstrated in any of the five

Common characteristics of the patients with spontaneous regression of varices were cessation of drinking of alcohol improvement of liver function in the majority rarity of splenomegaly and ascites and generally reduction of liver

9 A M A A h I t M d 9 507 5 O tobe 1953

the peritoneal cavity would remain dry This reasonin, was borne out by the results in none of the animals was any effusion found in the abdomen but in some instances peri hepatic effusion appeared in the thorax and the fluid which accumulated was similar in composition to ascitic fluid obtained after venous ligation without transposition of the liver

It thus appears that venous congestion of the liver parenchyma results in transudation through the capsule of Glisson and is the only mechanical factor capable of producing ascites Hepatic congestion is followed by lymphatic stasis in the portal region but since the ascitic fluid is hepatic in origin neither this stasis nor splanchnic vascular congestion can be considered factors in production of mechanical ascites

[Studies will have to be performed to determine whether the human cirrhotic liver also leaks significant amounts of a citic fluid—Ed]

Incidence and Diagnosis of Esophageal Varices in Cirrhosis of Liver Esophagoscopic Study carried out on 150 patients with histologically proved cirrhosis is reported by Irving B Brick and Eddy D Palmer[8] (Georgetown Univ) Re-

INCIDENCE OF ESOPHAGEAL VARICES BY ESOPHAGOSCOPY IN 150 CASES OF CIRRHOSIS OF LIVER

	Cases	%
Total	150	100 0
Esophageal varices	95	63.3
History of hemorrhage	59	39.3
History of hemorrhage with esophageal varices	47	31 3
No history of hemorrhage	91	60 6
No history of hemorrhage with esophageal varices	48	32 0

sults regarding the incidence of the varices are shown in the table Comparison of x ray and esophagoscopic findings for 147 patients showed 92 (62 5%) with varices by esophagoscopy and 19 (12 9%) with varices on x ray The 19 with varices on x ray also had a positive esophagoscopic result

In a recent textbook it was stated that since varices tend to rupture great care is necessary during esophagoscopy to avoid damage No untoward effects were noted in any of the 150 patients

The natural course of varices may be followed by endoscopy alone and certainly follow up study to evaluate the success of any current or proposed surgical procedures for portal

(8) Ga t oente ol gy 25 378-384 N mbe 1953

value rose from 26 5 ± 12 9% to 42 9 ± 12 5% a highly significant change

Hepatic arteriovenous oxygen difference increased following portacaval anastomosis in 9 of the 12 patients increasing an average of 4 1 ± 0 6 to 5 8 ± 1 5 ml /100 ml blood Calculation of total hepatic oxygen uptake from simultaneously determined values for EHBF and hepatic arteriovenous oxygen difference yielded figures (average 50 9 ± 13 9 ml /minute) which agreed with those obtained in other patients with cirrhosis There was no significant change postoperatively indicating an inverse correlation between EHBF and hepatic arteriovenous oxygen difference This calculation of hepatic oxygen consumption provides an estimate of the true value An undetermined volume of oxygen has been removed from the portal blood which contributes to the total hepatic venous outflow

Since portal venous pressure decreased in every instance at operation immediately after the portacaval shunt was opened the fall in EHBF observed as long as two years postoperatively was probably due to a persistent reduction in portal venous pressure The fall in EHBF may therefore be considered a reflection of diminished hepatic portal inflow modified to some extent perhaps by secondary changes in hepatic arteriolar resistance and hepatic arterial inflow

[The results of this study help explain why liver function tests may be unaffected or may improve following portal systemic shunt procedures in patients with hepatic cirrhosis —Ed.]

Blood Ammonia and Electrolytes in Hepatic Coma Robert Schwartz Gerald B Phillips George J Gabuzda Jr and Charles S Davidson[2] (Boston City Hosp) investigated the blood acid base electrolyte and ammonia patterns of 22 patients with advanced cirrhosis of the liver in an attempt to correlate chemical and clinical observations Only two patients were free from edema and ascites The patients were classified into (1) those with impending coma (clouded sensorium confusion disorientation and a coarse flapping tremor) and (2) those with coma (unresponsive to pain with occasionally absence of corneal reflexes and sometimes presence of tremor) Twenty of the 22 died in coma

Ammonia was expressed as micrograms of ammonia nitro

(2) J Lab & Cl Med 4 499 503 Oct be 1953

size Liver damage varied from mild to severe but tended to be less severe than in the control group with varices

The variability of portal pressures in cirrhosis may be the theoretical basis for the reported observations These fluctuations also may be a precipitating factor in hemorrhage from esophageal varices

Portal hypertension without esophageal varices causes few if any symptoms Surgery is warranted in portal hypertension only to provide freedom from hemorrhage Until it is proved that operation definitely decreases mortality every opportunity should be allowed for the spontaneous regression of varices before surgery is recommended

[Unfortunately no practical method is available for judging the relative accuracy of esophagoscopy and x ray in the diagnosis of varices To evaluate one method in terms of the other is an arbitrary assumption that one technic is sufficiently established to serve as the reference standard In addition the criteria used in making the diagnosis of cirrhosis are variable Despite these difficulties the two preceding reports contribute greatly to our knowledge of the incidence and course of esophageal varices —Ed]

Effect of Portacaval Shunt on Estimated Hepatic Blood Flow and Oxygen Uptake in Cirrhosis was studied by S E Bradley C M Smythe H F Fitzpatrick and A H Blakemore with A I S Macpherson and A Gammeltoft[1] In 10 of 12 patients with portal hypertension and cirrhosis estimated hepatic blood flow (EHBF) was measured by the bromsulfalein method before and after establishment of the portacaval shunt and in all 12 hepatic arteriovenous oxygen differences were measured The EHBF averaged 1 266 $\pm$ 282 ml /minute (range 940 1 780 ml) before operation It decreased in every instance preoperatively falling on the average to 845 $\pm$ 284 ml /minute (range 480 1 490 ml) These data were insufficient to permit accurate evaluation of the type of surgical procedure (end to side portacaval anastomosis in three side to side portacaval anastomosis in two and end to side splenorenal venous anastomosis in five) in terms of its effect on EHBF However the largest reductions were noted following side to side portacaval anastomosis and the smallest following splenorenal venous anastomosis With the fall in EHBF hepatic extraction of bromsulfalein increased in six patients and remained relatively unchanged in four On the average the

(1) J Cl I t 32 5 6 537 J 1953

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(2) J Lab & Cl Med 4 499 508 O t b 1953

gen per milliliter of whole blood and represents free ammonia as well as nitrogenous substances in blood capable of releasing ammonia Normal persons were found to have had a mean value of 2 04 (S D ± 0 45) The patients with cirrhosis but no neurologic complications had a mean level of 2 74 (S D ± 0 86) The mean level in impending coma was 4 32 and in coma 6 0 However individual values ranged from normal to highly elevated In serial observations neither tremor nor state of consciousness correlated well with blood ammonia values

Although the mean data for patients with hepatic coma indicated normal acid base equilibrium and electrolyte con centrations except for hypochloremia and hyponatremia the data varied greatly from patient to patient and no consistent biochemical picture was observed Despite the fact that sev eral patients had very low serum sodium and potassium levels neither acidosis nor hypokalemia was outstanding and no relationship between these substances and neurologic status was noted Azotemia was not noted initially nor did it develop as the patients progressed into coma

No one chemical abnormality was found to be of etiologic importance Serum electrolyte and pH changes were so in consistent that they argue against a correlation with coma No precise correlation was noted between blood ammonia values and degree of consciousness but the disturbance in ammonia metabolism although not established as causative correlates well enough to warrant further investigation

Episodic Stupor Associated with Eck Fistula in the Human with Particular Reference to Metabolism of Ammonia is dis cussed by William V McDermott Jr and Raymond D Adams[3] (Harvard Med School)

The portal vein was resected during pancreatoduodenectomy in a man 69 with carcinoma of the pancreas and the superior mesen teric vein was joined to the inferior vena cava thus producing a true Eck fistula During the next six months he had four spon taneous episodes of stupor consisting of periods of impaired alert ness and retarded responsiveness which varied in degree from mild confusion to coma There were no focal and lateralizing neurologic signs but uninhibited and senseless behavior fluctuating rigidity of the limbs reflex gra ping and sucking and bilateral extensor plantar reflexes were observed The episodes resembled hepatic coma in

(3) J Cli In e t 33 1 9 Ja ry 1954

many respects He was readmitted to the hospital for six months of study

Since elevated levels of blood ammonia have been demonstrated in dogs with Eck fistulas and neurologic disorders have been induced in patients with liver disease by administration of certain nitrogenous substances blood ammonia levels from day to day were determined The ammonia levels were consistently higher than normal even when the patient was mentally alert During hospitalization *eight episodes of stupor were induced by the administration* of excess protein urea ammonium chloride or resodec® (ammonium and potassium cation exchange resin) Urea produced the most severe episode The electroencephalogram correlated well with the clinical status of the patient by always reflecting the slightest mental aberration Concomitant with the clinical episodes of stupor was a sharp rise in the level of ammonia in the blood The patient was given not more than 40 Gm protein daily in order to control the blood ammonia level With this regimen he had only two brief episodes of mild confusion lasting one to two days in nearly four months

Although relatively little is known about metabolism of ammonia in man an adequately functioning liver is essential in mammals for elimination of ammonia All the sources of ammonia formation are not known but in addition to the processes of deamination within the body ammonia is formed within the gastrointestinal tract by the action of urea splitting micro organisms and presumably is absorbed in relatively high concentrations into the portal system When the liver is by passed by an Eck fistula relatively large amounts of ammonia entering the portal system from the gastrointestinal tract are not detoxified with sufficient rapidity to prevent elevation of ammonia concentration in the systemic circulation This elevated level of ammonia may interfere directly or indirectly with the metabolism of the central nervous system Although the onset of stupor is consistently correlated with high blood ammonia level the blood level falls rapidly when ingestion of ammonia containing compounds is discontinued whereas central nervous system symptoms continue for several hours or days Liver disease like an Eck fistula may interfere with normal conversion of ammonia to urea and thus impair cerebral metabolism

Effect of Glutamic Acid on Coma of Hepatic Failure was investigated by J M Walshe[4] (University College London) Glutamic acid is the only amino acid oxidized by the brain It

(4) Lancet 1 1075 1077 May 30 1953

enters the Krebs cycle as α ketoglutaric acid and thus glutamic acid is associated with carbohydrate metabolism It binds ammonia to form glutamine which is metabolized without liberation of free ammonia In view of the role of glutamic acid in both cerebral and hepatic metabolism and its action in removing ammonia which may be one of the toxins producing coma large intravenous doses of glutamic acid were given to patients in hepatic coma

Twenty grams of glutamic acid was neutralized with sodium hydroxide to give 23 Gm sodium glutamate in 80 ml water This solution was added to 500 ml of 5% glucose and given intravenously over three to four hours Too rapid administration leads to salivation flushing and vomiting

Beneficial effects were observed in three patients in five episodes of coma There was one failure On one occasion also the withdrawal of glutamic acid therapy appeared to precipitate coma The mechanism of restoration of consciousness is not clear The action is more likely cerebral than hepatic and possibly due to the ammonia binding power of glutamic acid Its action in the Krebs cycle may also be important Whatever its action glutamic acid is worthy of further trial in the treatment of hepatic coma

[The preceding three articles emphasize the recently reactivated hypothesis that ammonia or ammonia precursors may affect cerebral function when amines absorbed from the gastrointestinal tract are not detoxified or ammonia not changed to urea because the liver is damaged or by passed by vascular shunts Nonspecificity of the methods used for measuring blood ammonia however continues to be a problem If the hypothesis is correct it would appear that the body can establish compensatory and protective mechanisms for bouts of stupor do not occur in young patients who have persistent and high grade extrahepatic portal obstruction with extensive collateral circulation around the liver Unfortunately the brilliant idea that excess ammonia in nerve tissue might be bound by administering glutamic acid is not meeting with much clinical success in the treatment of hepatic coma —Ed]

Radioactive Iron Absorption in Siderosis (Hemochromatosis) of Liver Ralph E Peterson and Richard H Ettinger[5] (Walter Reed Army Med Center) used the balance technic to study absorption of physiologic amounts of orally administered Fe^{59} in five normal and two patients with siderosis one of whom had hepatic siderosis at the time of study and the other having had stored iron removed by previous phlebotomies Maximal serum concentrations were reached within two

(5) Am J Med. 15 518 524 Oct be 1953





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(Cou t y f P t R E d Ettı g R H Am J Med 15 518 5 4
Octob 1953)

hours Radioactive iron was recovered from the stool for three or four weeks however 99% of this was obtained in the first week

In a man 50 needle biopsy showed extensive portal fibrosis with pseudolobulation fatty metamorphosis and marked siderosis of the liver parenchyma (Fig 80) Serum iron content was 275 µg /100 cc and serum iron binding capacity was zero After 37 L blood containing 15 Gm iron had been removed in 61 phlebotomies serum iron level was 40 µg /100 cc and iron deficiency anemia was present. Liver biopsy showed no change in degree of fibrosis but the hemosiderin had disappeared (Fig 81)

The only reliable method for measuring iron absorption in patients with increased iron stores is by balance studies for absorbed iron goes directly to the liver for storage When the liver contains excessive iron only a fraction of that recently absorbed is utilized immediately for red cell production so red cell iron uptake is not indicative of absorption. The authors conclude that absorption is not necessarily related to body needs the defect in hemochromatosis is increased *iron absorption and no significant iron excretion occurs* Iron stores may be reduced by phlebotomy Compounds that form unabsorbable iron complexes such as phosphate salts should be given with meals

[The striking finding in this study is that removal of iron deposits from the liver is not necessarily accompanied by decreased hepatic fibrosis —Ed]

Genetic and Biochemical Aspects of Wilson's Disease *A G* Bearn[6] (Rockefeller Inst) after studying 26 patients in 16 families believes that Wilson s disease is inherited as a recessive None of the parents of affected individuals had overt Wilson s disease or any demonstrable biochemical abnormality In this series the disease occurred in 17 males and 8 females This deviation from 1 1 sex ratio is probably significant The probability of an affected issue from the union of an affected person and a genetically unrelated person is small and depends on the frequency of the abnormal gene in the general population Union between related persons greatly increases the probability of a meeting of the abnormal alleles When an individual is heterozygous for such an allele the probability of a first cousin having the same allele is 1 8 and a union has a 1 32 chance of producing a homozygous affected offspring Thus it is important to estimate the degree of con

(6) Am J M d 157 44 449 Oct b 1953

sanguinity in the affected families In the group studied 31% were Italian and 50% Jewish groups considered to have a high coefficient of inbreeding The incidence of first cousin marriages in the parents of 16 patients was 37 5% and total consanguinity rate was 62 5%

Increased tissue copper content especially in liver and brain increased urinary copper excretion aminoaciduria and decreased serum copper levels have been reported in patients with Wilson s disease In 17 patients serum copper level was below normal in 15 and in the low normal range in 2 Copper in serum exists as a firmly bound metalloprotein (coeruloplasmin) which has oxidase activity in vitro A direct relationship exists between serum copper levels and serum copper oxidase activity which was lower than normal in patients with Wilson s disease This reduction is marked and consistent Coeruloplasmin may not have enzymatic function in vivo If it is an enzyme its normal substrate is unknown Spectrophotometric and immunochemical technics revealed low coeruloplasmin levels in patients with Wilson s disease

Patients with various types of cirrhosis particularly biliary have increased urinary copper excretion However serum copper levels are normal to elevated the highest values occurring in biliary cirrhosis Therefore to have diagnostic significance with respect to Wilson s disease increased urinary copper excretion should be associated with low serum copper content

Characteristic biochemical abnormalities occur whether the disease exhibits predominantly hepatic or neurologic symptomatology Neurologic improvement following administration of BAL or versene (calcium disodium versenate) suggests that in the brain excess copper is only loosely bound whereas lack of hepatic improvement suggests excess copper in the liver is more firmly bound

Any unifying concept of Wilson s disease must explain an increased excretion of copper in the urine and a lowered serum copper level existing simultaneously as well as aminoaciduria without significant elevation of total plasma amino acids

Solitary Pyogenic Abscess of Liver Treated by Closed Aspiration and Antibiotics Report of 14 Consecutive Cases with Recovery is presented by A J S McFadzean K P S

Chang and C C Wong[7] (Univ of Hong Kong) This recognizable clinical entity appears to have an unusually high incidence in Hong Kong In addition to the 14 cases found among 2 868 hospital admissions 6 others not included in the study were seen in consultation The ages of the nine males and five



Fig 8 —P t te film tak n mm d t ly aft fir t a p r t on of 1 400 cc pus N t g g l ty of b ty (Courtesy of M Fad ean A J S f l B t J Su g 41 141 152 S pt mbe 1953)

females in the present series ranged from 1 to 50 most of the patients being under 30 Bacillus coli was isolated in pure culture in eight cases B coli and anaerobic streptococcus in one anaerobic streptococcus in pure culture in one Staphylococcus aureus in one and a hemolytic streptococcus in one the pus was sterile in two Pyogenic organisms may reach the liver via the portal vein biliary tree or hepatic artery by

(7) Brit J S g 41 141 15 S pt mb 1953

direct extension from an adjacent infectious process and by penetrating injury The route of invasion was the hepatic artery in 2 cases the original focus being in the tonsils and skin respectively in the other 12 cases no focus could be determined The identity of the organisms isolated in 10 of the 12 cryptogenic cases indicates that the primary focus was the gastrointestinal tract The right lobe was involved in 13 cases and the left lobe in 1

Average duration of symptoms was 18 days In 13 cases onset was insidious with fever and progressive severe general malaise Most patients had chills followed by an increase in fever profound malaise and pain Pain was due to distention of the liver capsule and was usually associated with epigastric distress It was aggravated by movement in 10 cases especially by lying on one or the other side and by inspiration in 5 cases All patients had lost weight Respiratory symptoms were present in eight Only one patient had jaundice and this was slight All had fever after chills and pain A visible rounded mass in the abdomen was present in two patients and three had localized firm edema of the right lateral thoracic wall extending on to the abdominal wall All but one patient had a palpably enlarged liver but none had an enlarged spleen In five patients x ray study revealed no lesion of the respiratory system In four x rays disclosed reduction or absence of diaphragmatic excursion with localized doming in one The lungs of the other four showed varying degrees of involvement in the right lower zone Average white blood cell count was 25 500 The blood culture was sterile in all cases

Diagnosis of solitary abscess of the liver is not difficult The correct diagnosis was made in 13 cases within 24 hours of admission One case was originally misdiagnosed as a rapidly growing primary liver carcinoma

All patients were treated by closed aspiration of pus from the abscess and replacement with air to reduce postaspiration pain Lipiodol* was introduced in some cases to demonstrate the abscess (Fig 82) Antibiotics usually penicillin streptomycin and/or chloramphenicol were administered systemically to all patients with positive cultures Penicillin and streptomycin were injected into the abscess cavities Volume of the initial aspirate range was 90-1,700 cc The number of aspirations in each case ranged from two to three Response

was good in all cases and complete resolution occurred There were no pleural or peritoneal complications

[Although not as common as in Hong Kong solitary pyogenic abscesses of the liver are also found in the United States and should be considered among the diagnostic possibilities when there is evidence of infection in or around the liver —Ed]

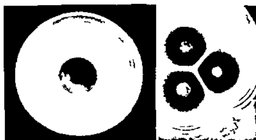
Experimental Studies on Colloid Chemical Mechanism of Gallstone Formation J Kleeberg[8] (Rothschild Hadassah Univ Hosp Jerusalem) states that colloid chemical factors as well as stasis infection or dyskinesia play a role in the formation of gallstones A gelatin dichromate silver nitrate and chloride experiment was set up as a model for gallstone formation in order to duplicate the colloidal and chemical factors of the gallbladder When a 2 3% gelatin layer containing 0 1% potassium dichromate is prepared on a glass plate and a drop of 50% silver nitrate solution is placed on its surface rhythmic Liesegang rings appear within 30-60 minutes (Fig 83) Similar periodic precipitation can be obtained when bile or serum is used instead of gelatin A large solitary stone can be produced when the end of a wooden stick wrapped with a few thin layers of cotton wool saturated with 25 or 50% silver nitrate is stuck into a 3% gelatin gel with 0 1% potassium dichromate and 0 03% sodium chloride Within one to two hours a mass develops containing a layered interior of brown concentric rings of silver bichromate and a white outer mantle of silver chloride Many objects can be used as the nuclei for stone formation in the gelatin dichromate silver nitrate and chloride preparation Faceted multiple model herd stones can also be produced by placing multiple cotton wool pellets saturated with the silver nitrate solution into the gelatin

The formation of rhythmic rings or periodic precipitations depends on four conditions (1) a colloidal substrate—a sol or gel (2) soluble crystalloids or colloidal substances which can react to form a precipitate (3) a state of supersolubility and (4) a gradient between concentrations of the different constituents Gelatin acts as the gel producing material while silver dichromate and chloride ions serve as the precipitate forming substances Silver nitrate is in a state of supersaturation in the gel

The gallbladder has the same colloidal and chemical fac

(8) G t oe t l g a 80 313 339 1953

tors as the model and gallstones form under the same condi tions The first stage of natural gallstones is a gelatinous jelly like substrate The protein content of bile transforms it into a gel like stage There is also a jelly precursor stage for renal stones The concentric laminated patterns of gallstones are comparable to the experimentally produced Liesegang rings Cholesterol and bile calcium salts can be precipitated by the immigration of positively charged blood proteins to the negative bile colloids their neutralization produces a dis integration of the colloidal phase—gel formation—and thus



F g 83 (l ft) —L g g g on g l t n film.
F g 84 (ght) —Th g wth t h w g t ght l nt f f mat on (Cou t y f Kl b g J G t oe log 80 313 339 1953)

changes supersaturation to supersolubility The pH is then changed to either a very acid or a very alkaline reaction Bile salts help keep cholesterol in a colloidal supersaturated solu tion During infection bile salts are reduced and the choles terol goes into a state of supersolubility which leads to precipitation in the form of crystals Bile pigments combined with calcium ions form insoluble salts These constituents precipitate in a rhythmic form

The round globular or barrel forms of the natural solitary large stones are the result of the colloidal and physicochem ical forces rather than mechanical pressure Surface tension and diffusion and adsorption forces in a colloidal biphasic system can cause one large stone The geometric polyhedric forms from multiple growth centers are the result of rhythmic precipitation of interference of surface tension and diffusion and adsorption forces (Fig 84) The formation of the numer ous polyhedric bodies with their concentric rhythmic inner

shells was completed within a matter of hours in experiments Precipitation of colloids is probably accomplished as rapidly as clotting of blood Multiple stones are probably formed from multiple nuclei in the gallbladder

It is possible that one night s biliary attack or even an attack of dyskinesia is enough to fill a gallbladder with a definite number of polyhedric pre formed jelly stones Their final shape and fate may be modified by mimesis by de hydration and by calcification—processes which may take considerable time

[The dynamics of gallstone formation is a long neglected field The results of this study are impressive but one may wonder whether a static model can in any way imitate conditions within a gallbladder where changing volumes pressures and flows are constantly at play The concept that gallstones can form so to speak overnight may be novel to many —Ed]

Visualization of Bile Ducts with Biligrafin (Schering) Eva Gaebel and Werner Teschendorf[9] (Cologne) call atten tion to a new contrast medium biligrafin an iodine containing

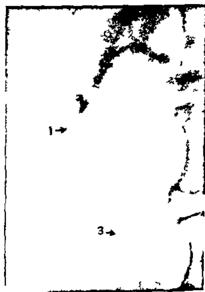


Fig 85 —Bile ducts (1 hepatic duct 3 common bile duct) of cholecystectomized patient 10 minutes after injection of biligrafin (Courtesy of Gaebel E. and Teschendorf W Röntgen Blatt 6 162 170 July 1953)

(9) Rontgen Bl tt. 6 162 170 July 1953

substance given intravenously with which the gallbladder can be visualized within two hours after injection In a patient with previous cholecystectomy the bile ducts will be seen in 10-40 minutes (Fig 85) Nausea and vomiting have occurred occasionally The dye sometimes appears in the renal pelves particularly if hepatic secretory function is impaired

Use of this medium is indicated (1) after cholecystectomy when there are symptoms referable to the bile ducts such as may be produced by stones and inflammation (2) when stones are suspected in the bile ducts and (3) when oral contrast mediums fail to visualize the gallbladder In cases of the last type biligrafin has often been successful in filling the gall bladder and revealing stones

[The dye marketed in this country under the name cholografin (Squibb) has been used successfully in the United States without serious side reactions (Am J M Sc 227 361 1954) In jaundiced patients however when the secretory activity of the liver is impaired either by parenchymatous disease or advanced obstruction of the biliary passages biligrafin cannot be expected to outline the bile ducts or gallbladder —Ed.]

Cholecystography in Portal Cirrhosis without Jaundice

Charles L Cuniff Mario A Dolan and Carroll M Leevy[1] (Jersey City N J Med Center) did cholecystographic studies among 50 patients with portal cirrhosis without jaundice to correlate the visual with the clinical biochemical and histologic observations For contrast studies 6 tablets telepaque® were used and if cholecystographic visualization was poor 12 tablets were given in a second attempt Visualization was considered good in 28% poor in 40% and lacking in 32% unsuspected gallstones were found in 18% In two patients the contrast medium caused nausea vomiting and diarrhea Delayed toxic effects were not noted in patients with non visualized gallbladder

The severity of clinical changes and the visualization of the gallbladder were directly correlated Ascites high levels of bromsulfalein retention strong cephalin flocculation and biopsy evidence of pronounced fibrosis often accompanied nonvisualization of the gallbladder

In five patients with gallstones four poorly and one not at all visualized operation confirmed the diagnosis no one died Severe temporary clinical and biochemical deterioration occurred with surgery The degree of change in function was sufficient to contraindicate elective surgery

(1) G t ent l gy 5 557 564 D mbe 1953

Nonvisualization of the gallbladder in portal cirrhosis is more common than in other hepatic diseases in severe liver disease it is due to decreased hepatic reserve Cholecystitis cholelithiasis or other nonhepatic factors cause nonvisualization *if there are minor liver changes*

Problem of Hepatolithiasis Study of 35 Personal Cases was made by N Frederick Hicken A James McAllister and Dee W Call[2] (Univ of Utah) A review of the literature revealed reports of intrahepatic bile duct stones in 5 66 83 and 9% of patients with cholelithiasis In 1944 Best reported that hepatic calculi occur in about 7 4% of all patients with



Fg 86—F e to w mo ed f m mm n b l d ct and T t be was i se t d Cholang ogram m d n p t g tabl d l d lcul l ft hep tic duct Tub w s t k n t a d ston m d (C t y f H k N F t l Am Su ge n 19 695 707 A gu t 1953)

(2) Am S g 19 695 707 A g t 1953

cholelithiasis The stones are most often of the bilirubin calcium variety but vary in size shape and consistency Often they consist of agglomerate masses of biliary sand and inspissated bile pigments congealed by a matrix of viscid mucus Diagnosis is difficult as shown by the fact it was not made preoperatively in any of the authors 35 cases Clinically intrahepatic calculi are indistinguishable from extrahepatic biliary calculi Roentgenography affords the only method for preoperative diagnosis Liver stones produce hazy indistinct opaque patterns Mulberry like shadows and diffuse studding have been reported Operative cholangiograms successfully visualized intrahepatic calculi in 51% of the present series (Fig 86)

The chief menace of intrahepatic stones is their tendency to migrate into the common bile duct Initiation of free bile flow after operative release of biliary obstruction flushes them into the common duct where they are in a position to cause trouble Postoperative cholangiograms have outlined patent common bile ducts but subsequent cholangiograms made before new stones could form have demonstrated calculi within the choledochus Of the 35 patients with hepatolithiasis 15 have required subsequent operation for choledochal obstruction Suspicion of hepatic calculi should be aroused if the extrahepatic ducts contain small stones biliary sand or inspissated bile pigments if one segment of the liver is enlarged cirrhotic and bile stained if there are localized liver abscesses and if calcified shadows appear on the roentgenograms

[Rarely stones occur in the liver without being found in the gall bladder This condition apparently obtained in 1 of the 35 cases here reported —Ed]

Antibiotics in Disease of the Biliary Tract Jerry Zaslow[3] (Albert Einstein Med Center) found that the excretion and concentration of the sulfonamides penicillin streptomycin chlortetracycline and oxytetracycline in the abnormal biliary tract were entirely different from those in the normal In the presence of impaired liver function or common duct obstruction or both the drugs were either not excreted or excreted in only small amounts When the cystic duct was patent and the drugs were excreted by the liver they appeared in the gall bladder bile When the cystic duct was obstructed none of the

(3) J A M A 15 1683 1686 A g 29 1953

agents entered the gallbladder lumen regardless of the state of the organ

Clinical studies were undertaken in 171 patients with acute cholecystitis Half the patients received an antibiotic It appears that antibiotics did not affect the local pathologic changes Local tenderness and rigidity were decreased but a palpable mass persisted and empyema was seen in 16% of treated and untreated patients Systemic symptoms were promptly relieved and Zaslow considers antibiotics useful in acute cholecystitis when there is severe systemic reaction However since the local pathology is unaltered the physician must not be deluded into a false sense of security

Eighty four patients with common duct obstruction were similarly treated At operation positive bile cultures were found in 85 7% of the treated and 82% of the untreated group Because the liver is exceedingly vascular antibiotics reach it in high concentration In many patients with obstructive jaundice and cholangitis antibiotics improved the general condition so that preoperative preparation was more effective Systemic reaction is produced by invasion of the liver and subsequently the blood stream The antibiotics seem to arrest the organism at the hepatic level converting a general disease to a local one

[In patients acutely sick and febrile because of biliary tract disease antibiotics in large doses appear indicated whether or not they can penetrate to the primary site of infection They are helpful in holding the inflammatory process in check until such time when the obstruction often associated with biliary tract infection subsides and again permits biliary flow —Ed]

Abnormal Electrolyte Composition of Sweat in Cystic Fibrosis of the Pancreas Clinical Significance and Relationship to the Disease Paul A di Sant Agnese Robert C Darling George A Perera and Ethel Shea[4] (Columbia Univ) found that the electrolyte composition of sweat secreted in response to a standard mild thermal stimulus was abnormal in 43 patients with cystic fibrosis of the pancreas Sodium and chloride concentrations in sweat were two to four times as high as in 50 patients with a variety of other diseases Sweat potassium levels were also increased though not to the same extent The amount of sweat was not significantly dif

(4) Pediatrics 12 549 563 November 1953

ferent in patients with fibrocystic disease of the pancreas and control patients Pancreatic deficiency chronic pulmonary disease and administration of pancreatic extracts or oxytetra cycline did not in themselves elevate the electrolyte concen tration of sweat In patients with fibrocystic disease the be havior of the kidney following salt restriction and of the adrenal following administration of corticotropin is different from that of patients with nephritis or Addison s disease and excludes these two organs as cause of the high sweat electro lytes in this condition The dissociation of increased electro lytes in the sweat and low sodium and chloride levels in the urine during periods of low salt diet appears to be a unique characteristic of cystic fibrosis of the pancreas

The finding that the sweat glands do not retain salt effec tively in hot weather during salt restriction or when DCA is administered points to a disturbance in the sweat glands themselves It is not known whether abnormally high elec trolyte content of the sweat is pathognomonic of fibrocystic disease of the pancreas Disturbances in sweat composition and observations that the saliva is secreted at a high rate and contains elevated concentrations of sodium and chloride sug gest that the secretory activity of many and perhaps all exocrine glands is affected in cystic fibrosis The term muco viscidosis does not seem justified in view of the fact that at least two non mucus secreting structures are affected in this condition

Massive salt loss through sweating in hot weather ac counts for the heat casualties in cystic fibrosis The symp toms are initiated by pure salt loss and consequent reduction in extracellular fluid volume This condition must be treated as an acute medical emergency and the depleted water and electrolyte stores must be restored

In usual circumstances serum electrolyte concentrations are normal in fibrocytic disease In the presence of marked pulmonary dysfunction the bicarbonate plasma content is elevated and the chloride content reduced in compensation It is therefore necessary to demonstrate a lowered serum sodium as well as chloride content to detect the massive salt loss which may occur in hot weather

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Clinical studies were undertaken in 171 patients with acute cholecystitis Half the patients received an antibiotic It appears that antibiotics did not affect the local pathologic changes Local tenderness and rigidity were decreased but a palpable mass persisted and empyema was seen in 16% of treated and untreated patients Systemic symptoms were promptly relieved and Zaslow considers antibiotics useful in acute cholecystitis when there is severe systemic reaction However since the local pathology is unaltered, the physician must not be deluded into a false sense of security

Eighty four patients with common duct obstruction were similarly treated At operation positive bile cultures were found in 85 7% of the treated and 82% of the untreated group Because the liver is exceedingly vascular, antibiotics reach it in high concentration In many patients with obstructive jaundice and cholangitis antibiotics improved the general condition so that preoperative preparation was more effective Systemic reaction is produced by invasion of the liver and subsequently the blood stream The antibiotics seem to arrest the organism at the hepatic level converting a general disease to a local one

[In patients acutely sick and febrile because of biliary tract disease antibiotics in large doses appear indicated whether or not they can penetrate to the primary site of infection They are helpful in holding the inflammatory process in check until such time when the obstruction often associated with biliary tract infection subsides and again permits biliary flow —Ed]

Abnormal Electrolyte Composition of Sweat in Cystic Fibrosis of the Pancreas Clinical Significance and Relationship to the Disease Paul A di Sant'Agnese Robert C Darling George A Perera and Ethel Shea[4] (Columbia Univ) found that the electrolyte composition of sweat secreted in response to a standard mild thermal stimulus was abnormal in 43 patients with cystic fibrosis of the pancreas Sodium and chloride concentrations in sweat were two to four times as high as in 50 patients with a variety of other diseases Sweat potassium levels were also increased though not to the same extent The amount of sweat was not significantly dif

(4) Pedi t cs 12 549 563 N vembe 1953

40% of the dietary intake of oleic acid or as much as that of dietary lard It follows that bile is needed for the absorption of fatty acid but not for the hydrolysis of triglyceride To correct steatorrhea in the dog with a biliary fistula fresh bile must be passed into the duodenum hourly instead of every four or eight hours Required total bile dosage nearly equals the steady bile output of the intact dog

Conjugated bile salts glycocholate taurocholate and taurodesoxycholate are satisfactory substitutes for fresh bile in the dog with fistula and these conjugated salts in bile appear to account completely for the facilitated assimilation of dietary triglyceride More than 12 Gm daily is required for complete replacement of bile in the dog Sodium cholate and desoxycholate are poorly tolerated oxidized cholate does not facilitate lipid absorption and sorethytan mono oleate does not alter fecal excretion of lipid in the dog with biliary fistula

Vitamin K Requirements of Adult Dogs and Influence of Bile on Its Absorption from the Intestine were studied by Armand J Quick Clara V Hussey and George E Collentine Jr[6] (Marquette Univ) They found cholecystonephrostomy a practical technic since loss of bile through the kidney and its absence in the intestine decreases absorption of vitamin K so drastically that severe hypoprothrombinemia is produced The adult dog requires about 0 5 μ vitamin K_1/kg to maintain a normal level of prothrombin If the vitamin K requirements in man equal those in the dog 500 mg would supply the metabolic need of the adult man for about 20 years In the dog bile unless given in large doses (5 ml fresh ox bile/kg or 12 Gm desiccated bile) was ineffective in causing absorption of sufficient vitamin K_1 from the diet to restore normal prothrombin concentration

The metabolic requirement of vitamin K_1 is very small but quite finite and under controlled conditions constant Poor absorption of natural vitamin K_1 from the intestinal tract is an important factor in hypoprothombinemia The normal person with adequate production of bile may absorb only slightly more vitamin K_1 than is required daily to maintain a normal concentration of prothrombin

The erroneous claim that menadione has three times the

(6) Am J Phy I 176 39 24 F bru y 1954

Function of Pancreatic Juice and of Bile in Assimilation of *Dietary Triglyceride* Review John H Annegers[5] (Northwestern Univ) evaluated gastrointestinal assimilation of *dietary lipids* in normal subjects in those deprived of pancreatic juice and in those deprived of *bile* *Balance studies compared total fecal excretion* with the range of dietary lipid intakes

In normal man fecal lipid increases in approximately linear fashion with dietary triglyceride (0 03 Gm fecal lipid/ Gm ingested) when all dietary constituents are increased but substituting lipid for carbohydrate does not change fecal *lipid* excretion Man excretes an estimated 2 Gm fecal lipid when the diet contains no triglycerides It appears that normal *man* absorbs ordinary triglycerides completely and that fecal lipid is usually of endogenous origin In the absence of pancreatic juice about 60% and in the absence of bile about 40% of a physiologic lipid intake is assimilated in the dog and *roughly* 30% and 50% respectively in man In neither condition is endogenous fecal lipid excretion significantly altered from normal After triglyceride intake the exogenous fecal lipid appears to be about 06% unsplit in the absence of pancreatic juice whereas in the absence of bile little or none of it is unsplit This suggests that pancreatic juice is necessary to normal triglyceride hydrolysis that fatty acid is a more readily absorbed lipid than triglyceride when pancreatic juice is absent and that bile is necessary to normal absorption of fatty acid

With the pancreas removed the dog fails to assimilate oleic acid normally suggesting an extradigestive function of the pancreatic juice A physiologic amount of $NaHCO_3$ satisfactorily replaces this extradigestive function it does not however improve the assimilation of dietary lard in the depancreatized dog

Whether or not pancreatic juice has some additional vital extradigestive function in the assimilation of dietary triglyceride is not known Dogs with biliary fistula assimilate about

(5) *A M A A ch I t Med 93 9 22 J n y 1954*

with a moderately high protein content is unanswered Evidence suggests that there is no advantage to the former Some believe excretion of large amounts of nitrogenous waste is an added stress The expectation that fat would be poorly

COMPOSITION OF FORMULAS FOR TUBE FEEDING

	Am t Gm				
	T t l	P l	F t	C rho-h d	Lact se
T be-Feeding F rm l 1					
E p ted kim milk	1 000	0		00	200
Skim milk powde	200	7°	2	104	04
Eg y lks	00	16	32	1	
S	100			00	
S lt	8.5				
W ter nd lt ml supplement †					
T l		158	34	305	304
T t l l ries 2 1.0					
T tal l m ,500 cc ‡					
Tube Feeding F rm l					
Milk wh le	000	3ɔ	39	49	49
Skim milk po d	90	32	9	46 8	46 8
E wh le	200	25.6	23	1 4	
Dextri-M ltose N 1	100			100	
Cre m, 20%	200	5 8	40	8	6
S lt	3 0				
Vit mi suppl me t †					
T t l		98	103	20ɔ	104
T l lori 2 k0					
T t l l me ,500 cc ‡					

Total od m tent f b th f m l w pp x mat ly 150 mEq /1 500 f m l

† V tam ppl ment w t kon (Upj h) 5 cc /1 500 c. f rm l Th ta d 2 mg th m 3 mg b fl 30 mg n cin d 100 mg b a d

‡ V l m f 1 500 w th al c l f 2 150 w th m t dm st d n 24 hou

tolerated was not borne out Diet 2 contained three times as much fat as diet 1

[This probably one of the most significant articles to appear during 1953 The science of nutrition has been so dominated by studies of the metabolic needs of the organism that the capacity and the function of the gastrointestinal tract have been totally ignored. When gastrointestinal tubes are used for feed ng and the barriers of taste and appetite thus circumvented such a potent concoction of nutrients and digests is often introduced as to overwhelm the tolerance of the alimentary canal which *for self protection has no other recourse than to empty itself as fast as* poss ble in both directions This art cle from the Mayo Clinic should prov de an effective antidote to such practices —Ed]

Celiac Disease—*I Criticism of various methods of investigation*—H A Weijers and J H van de Kamer[8] (Utrecht) find that in many clinics it is customary to form an opinion on the degree of fat absorption from microscopic observations

(8) A t p ed t 42 24 33 J ry 1953

potency of natural vitamin K_1 can be attributed to a difference in absorbability In prothrombinogenic potency vitamin K_1 ranks first but menadione bisulfite and synkayvite® are only slightly less powerful These agents have value in correcting hypoprothrombinemia of the newborn and in obstructive jaundice since all are absorbed without bile Natural vitamin K_1 is much more potent than synthetic compounds in counter acting such antivitamin K drugs as dicumarol®

The therapeutic value of bile in usual dosage (several grams a day) should be re evaluated in the light both of vitamin K_1 absorption and of other accessory fat soluble food factors

[From the practical viewpoint the gist of this report is that the substances hykinone® and synkayvite® should be used when vitamin K deficiency and hypoprothrombinemia are treated by the oral route—Ed]

Tolerance to Nasogastric Tube Feedings Comparative Clinical Study of Two Dietary Formulas was undertaken by Elizabeth B Smith and Eric E Wollaeger (Mayo Clinic) and Sister Mary Victor[7] (St Mary s Hosp Rochester Minn) The standard Mayo Clinic tube feeding formula 1 was compared with a *specially devised feeding formula 2 (table)* Intolerance was evidenced by diarrhea four or more watery movements a day

Diarrhea occurred in 39% of 44 patients on formula 1 and in 10% of 30 patients on formula 2 Ten of 12 patients receiving both feedings had diarrhea only with formula 1 and 2 patients had diarrhea with both formulas The cause of poor tolerance to formula 1 is not evident but may be related to its *high protein or carbohydrate content* the nature of the protein or carbohydrate or its unbalanced composition in the three major foodstuffs Frequency of diarrhea with formula 1 was a disadvantage outweighing the questionable advantage of high protein content Formula 2 was satisfactory for use

Routine tube feedings vary greatly in composition and caloric content carbohydrate 96-409 Gm , protein 60 140 Gm fat, 14 177 Gm Little attention has been paid to the possible adverse effects of carbohydrate Customary oral digestion is absent hence too much carbohydrate may produce untoward symptoms Whether an extremely high protein diet is more effective in maintaining nitrogen balance than a diet

(7) A.M A A ch Int. M d 91 721 728 J 1953

only apply when the diet contains sufficient fat For instance when buttermilk is given a child who with ordinary milk has a CA of 95% values varying from 50 80% are found This is simply a consequence of the fact that the influence of the endogenous fat on the CA becomes greater when the quantity of fat taken up with the food is small

On the assumption that absorption of fat soluble vitamin A parallels the absorption of fat the authors compared the

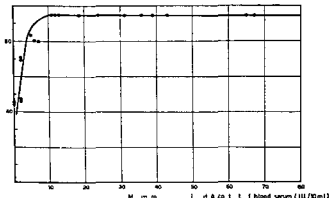


Fig 88—C l t f ffi t f f t b pt with m m l n ea n t m n A t t f bl d ft g g l t t d (10 000 I U t m n A/kg body w ght) (C t y f W j H A t d K m J H A ta p d t 4 24-33 J n y 1953)

coefficient of fat absorption with the vitamin A tolerance curve in several children with the results summarized in Figure 88 It appears that a rise of at least 10 I U /10 ml signifies good fat absorption for the rest however no conclusions can be drawn from progression of the curve as to the severity of the fat absorption defect

II Presence in wheat of factor having deleterious effect in cases of celiac disease—To determine why wheat in the diet of a patient with celiac disease may cause anorexia vomiting and diarrhea W K Dicke Weijers and van de Kamer[9] studied patients placed on a diet consisting of milk (standardized at 2 5% of fat) or protein milk eggs lean meat butter margarine vegetables fruit juices sugar glucose and cereals

(9) A t p d t 4 34 4 J ry 1953

of the fat in the feces Although this method is simple its correctness accuracy and reproducibility leave much to be desired as is plain when results of microscopic observations are compared with those of chemical determinations (Fig 87) *In the extreme cases 0 3% and >9% fat 60 70% of the* observations agreed with the chemical determination as to the fecal fat content when the fat content was 3 9% agreement was only about 40% Moreover the differentiation much medium and little is not very precise Even if

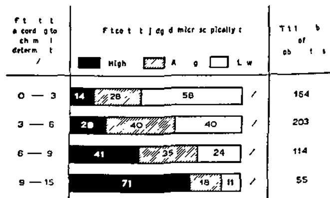


Fig 87—F t c t nt f f es det m n d h m cally nd m scop cally (Court sy f W) H A d v n de K mer J H Acta p ed at 4 4-33 Janua y 1953)

the fat content is correctly estimated conclusions regarding the degree of absorption cannot be based on this value only To determine exactly the fat content of the feces by chemical analysis the amount of the feces must also be considered

Determination of the coefficient of absorption (CA) expressed in percentage is helpful in assessing the fat absorption

$$CA = \frac{\text{Gm ingested fat} - \text{Gm excreted fat}}{\text{Gm ingested fat}} \times 100$$

Chylomicrograph and chemical determinations of the fat content of blood are useless in assessment of fat absorption

For adults a normal CA is 95% or more With regard to young babies it appears that the younger a normal baby the more likely is the CA to be about 85% An exception is the breast fed baby which always has a high CA These values

being calculated in grams/day As the amount of fat ingested was known the fat absorption coefficient could be calculated

Each diet period lasted three to four weeks—long enough to give the patient a chance to become adapted to the new diet i e to reach a new level if necessary This is usually attained after 10 14 days but may take longer Further it is necessary to obtain sufficient data at the new level to permit a statistical analysis Results in one case are shown in Figure 89

It was found that while wheat flour had a deleterious effect wheat starch did not Wheat starch is obtained by washing out kneaded wheat flour and allowing the starch to settle out of the washings after which it is dried Since the starch does not produce the harmful effect one of the other components of wheat flour unknown at present and called the wheat factor must be responsible In addition to wheat flour rye flour and oats have an unfavorable effect

It is probable that this wheat factor is active over a wider field than in celiac disease Some infants and young children with dyspepsia and subactute enteritis respond favorably to the wheatless diet Exact laboratory proof however is not yet available Not all forms of steatorrhea (fibrosis of the pancreas) are influenced by the wheat factor It remains to be seen whether the difference in behavior with respect to wheat will form a useful basis for a common classification into which celiac disease and related diseases can be placed

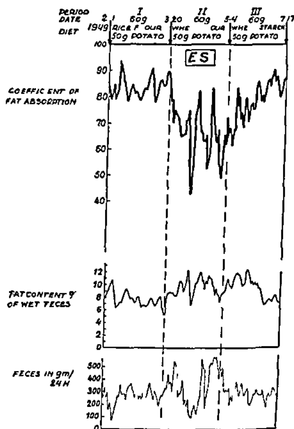
Obviously behind the alleged deleterious influence of carbohydrates on absorption there is another still unknown harmful food constituent which exerts its damaging activities in the patient with celiac disease either in the intestinal wall or deeper in the organism

III Excretion of unsaturated and saturated fatty acids by patients with celiac disease—Weijers and van de Kamer[1] state that although it is true that the coefficient of fat absorption (CA) and the amount of fat excreted in Gm /24 hours are good standards for judging the severity of steatorrhea in celiac disease they do not give sufficient insight into the nature of this symptom Differentiation of the fecal fat into saturated and un aturated fatty acids has more to offer in this respect

Because of the observations that more saturated than un

(1) Act p d 42 97 11 M h 1953

and/or starches in measured amounts for each patient Only the kinds of starch containing foodstuffs were varied but always in equivalent amounts with respect to starch content the other components of the diet remained unchanged Some



F g 89 —Eff ct f ta h c t g f ods (C rtesy of D ke W K et al Acta paed at 42 34 42 January 1953)

times a correction was made for the different protein contents of the various cereals and starches by varying the amount of lean meat

Every day or every second day the amount of feces/24 or 48 hours was measured and the fat content of the wet stools determined by the method of van de Kamer the fat excretion

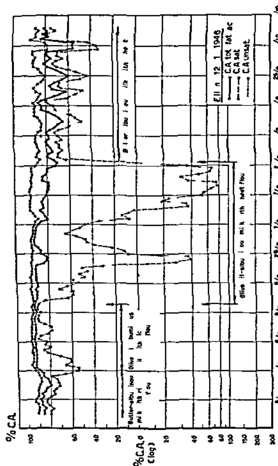


Fig 90 —Coeffi t f b pt f total fatty ds a d t ted and us tur t d fatty a ds n p t t th l d d t o t ng e ff t r pl d w th wh t fl d l nd M tt f t p t ly (C te y f W j s H A d de Kam J H Acta p d t 42 97 112 1953)

with regard to dry substance Whether abnormal liposynthetic micro organisms play a role in the fat excretion observed in celiac disease is being investigated

Because the high excretion of saturated fatty acids can not be explained on the basis of bacterial conversion the authors concluded that lipid excretion exists in patients with celiac disease who use wheat flour This was confirmed by

saturated fatty acids are excreted in celiac disease and that the coefficient of absorption of the saturated fatty acids declines first in parenteral infections the effect of substituting olive oil (high unsaturated fatty acid content) for butter (more saturated fatty acids) in the diet of patients with celiac disease was studied The experiments were carried out with diets which contained no wheat flour but rice flour and potatoes Olive oil immediately caused a rise in CA of the collective fatty acids from 85% to a normal 95% As few saturated fatty acids were administered with olive oil the CA was de termined practically only by the CA of the unsaturated fatty acids When the CA of the unsaturated fatty acids was con sidered separately it was evident that their CA was slightly higher when oil than when butter was used despite the fact that a diet with olive oil contains almost twice as much un saturated fatty acids Clinically the patients ingesting olive oil showed a distinct improvement in general condition activ ity increased color was better and indications of vegetative lability were less while the stool was practically normal as regards odor color and consistency

The CA of the unsaturated fatty acids was considerably higher than the CA of the saturated fatty acids on a wheat butter diet as well as on one with wheat olive oil and also on the respective rice flour diets While excretion of the unsatu rated fatty acids was not increased excretion of the saturated fatty acids was considerably raised by use of wheat flour With the consumption of olive oil even more saturated fatty acids were excreted than ingested which means a negative CA of saturated fatty acids (Fig 90)

From the fact that more saturated fatty acids were ex creted with the feces than were taken up with the food it fol lowed that impaired absorption did not provide a complete explanation One possibility is that intestinal bacteria convert unsaturated into saturated fatty acids It is highly improbable however that the bacteria regularly occurring in the feces should contain 5 7 Gm fat On a fat free diet the stools weigh no more than 200 Gm /day Since this amount cor responds to about 40 Gm dry substance and normally con tains 10 15 Gm dry bacterial soma half of the dry bacterial soma would have to be fat This is most unlikely because the normal fecal microflora contain only about 5% fat calculated

intestinal films showed hypermotility and an extremely coarse pattern in all segments of the small bowel suggestive of edema due to hypoproteinemia. Steatorrhea was diagnosed when 56, 8 and 60% fat was found in three dried 72 hour stool specimens. Peritoneoscopy and liver biopsy disclosed no abnormalities. Values of total serum protein were 3.8 Gm./100 cc. serum, of protein bound polysaccharides 5.25 mg./100 mg. protein (normal 2.5 ± 0.44) and of



Fig. 91.—Section of small intestine showing deeply stained granules with foamy cells. M. Ma... stain. (C... of Story, R. D., and S...gild, L.: J.A.M.A. 152:312-317, May 23, 1953.)

serum glycoprotein 260 mg./100 cc. serum (normal 9.. ± 21). Fat emulsions intravenously were poorly tolerated. For the last four weeks of life 50-400 mg. cortisone was given intramuscularly daily. The steady slow downhill course remained unaltered.

At autopsy the mucosa and wall of the small intestine were edematous and brawny. The mucosa had fissures with prominent white villous folds. A white greasy pastelike substance could be expressed from the cut surface. Many enlarged mesenteric nodes were found and the cut surface was of honeycombed pale gray

experiments showing that on a fat free diet containing wheat flour considerable quantities of fat were excreted with the feces and it is likely that a similar disturbance in intermediary fat digestion occurs in celiac patients consuming a wheat free diet

[Because the authors of these papers devised a practical and satisfactory method of fecal fat analysis and because they were willing to use it assiduously they have been able to elucidate the physiology of normal fat absorption analyze the abnormalities of absorption characteristic of the celiac syndrome and introduce specific dietary treatment of that disorder In adults with idiopathic sprue it appears at present that some are greatly benefited by omission of wheat from the diet but others do not improve until glucose sucrose and all starches are omitted and a final group appears to derive little benefit from any dietary measures—Ed]

Whipple's Disease (Intestinal Lipodystrophy) and Serum Glycoproteins are discussed by Robert D Story and Uffe Sagild (Boston) who report an antemortem diagnosis The disease characteristically occurs in middle aged men whose symptoms include vague gastrointestinal disturbances progressive loss of weight and strength and usually diarrhea arthralgia and chronic cough Often they have brown pigmentation of the skin and hypotension suggestive of Addison s disease The course is occasionally febrile and generalized lymphadenopathy suggesting infection may be noted Patients die one to five years after onset of symptoms Steatorrhea anemia and hypoproteinemia are present Normal or flat dextrose tolerance curves achlorhydria and hypocalcemia are common and occasionally persistent leukocytosis or eosinophilia is noted The small intestines and mesenteric lymph nodes have a characteristic appearance often with fibrous panserositis The phagocytosed substance in the foamy cells is nonsudanophilic and has characteristics of glycoprotein

Man 64 had lost 35 lb in two years For two months he had had a sense of abdominal fulness after meals and sometimes slight gripping pain in the epigastrium He had no anorexia but was afraid to eat because of the postprandial symptoms Glossitis was not present For four weeks the stools had been loose grayish yellow and occasionally looked like fat No blood was noted Fresh fruit or fruit juices caused bloating and bowel movements relieved abdominal discomfort The abdomen was distended and of doughy consistency The liver was not palpable

The ECG tracing indicated low voltage premature ventricular beats depressed S T segments in leads II and III low T_1 waves and right axis deviation X ray disclosed a normal chest Gastro

( ) J A M A 152 312 317 M y 23 1953

The primary pathologic processes of regional enteritis are increase in number of goblet cells lymphatic dilation tubercles and possibly diffuse cellular infiltration by plasma cells and lymphocytes Secondary inflammatory processes include mucosal ulceration thickening of the muscularis mucosae fibrosis and infection

Common symptoms and signs are shown in Table 1 Mucosal ulcerations of the rectum and sigmoid were found in



Fig 9 — Th ken g f m t ry g l te t (C rt y f V n P tt W N G t oent r logy 26 347-450 M h 1954)

56 patients who did not have x ray evidence of large bowel involvement This suggests that rectal and sigmoidal disease may occur apart from the main lesion of regional enteritis Localized lesions in the large bowel occurred in 16 patients with internal fistulas from the small intestine to the large bowel X ray evidence of involvement of the terminal portion of the ileum was found on barium enema in 91% in 41% of these the disease also involved portions of the adjacent colon

Of 187 patients who had appendectomy 23 5% later had

tissue with slight brown discoloration Thickening and clubbing of mucosal villi of the small intestines were due to diffuse but dense infiltration by large pale staining cells with granular or foamy cytoplasm Sections of the small intestines and nodes contained sudanophilic fat in large globules or aggregates of small globules Sudan stain of the foamy cells failed to disclose neutral fat but McManus stain for glycogen mucoproteins or glycoproteins disclosed numerous red violet granules within phagocytic cells in the intestines and lymph nodes (Fig 91)

Black Schaffer proved that Whipple s disease was not simply caused by blockage of lacteal or mesenteric lymph nodes but that the macrophages in the intestinal mucosa and lymph nodes contain glycoproteins The authors case confirms this observation Increased serum glycoprotein values in this patient did not account for the sharp increase in total protein bound polysaccharides so there must be an absolute increase in the polysaccharide bound to protein Although conclusions cannot be drawn from one case the simultaneous disturbance of intra and extracellular glycoproteins may have unsuspected significance Cortisone failed to help fecal fat content remained unchanged by therapy and the patient denied any subjective improvement

Regional Enteritis Ward N Van Patter J Arnold Bargen Malcolm B Dockerty William H Feldman Charles W Mayo and John M Waugh[3] (Mayo Clinic and Found) reviewed cases of 334 males and 266 females with regional enteritis during 1912 30 Age of onset varied from 4 to 74 in 55 3% it was 16 30 The ethnic derivation of patients was North European in 71 3% and Hebrew in 25 5% Of 342 patients operated on 21 3% had external fistulas 23 7% internal fistulas 11 4% multiple internal fistulas and 7 6% both external and internal fistulas

The most prominent gross pathologic feature was tremendous thickening of the bowel wall especially the submucosa and of the adjoining mesentery which often was 1 cm or more in thickness (Fig 92) Characteristic mucosal ulcers were observed usually along the mesenteric border and often dividing the mucosa into isolated islands of epithelium Microscopically edema fibrosis lymphatic dilatation cellular infiltration tubercles and pronounced thickening of the muscularis mucosae were evident

(3) G st oente ology 26 347 450 M ch 1954

controlled Of 400 surgical patients 37 had partial exclusion 27 complete exclusion 94 two stage resection 230 primary resection 10 ileostomy 1 partial exclusion with ileostomy 3 gastroenterostomy and 1 partial exclusion and resection In a total of 564 procedures the surgical mortality was 3.5 per cent After a minimum follow up period of two years the percentage of arrested cases was as follows partial exclusion —32 per cent complete exclusion—42 per cent partial exclusion resection—29 per cent complete exclusion resection—27 per cent and primary resection—33 per cent Partial or com

TABLE 2—EFFECT OF SURGICAL MEASURES FOR INITIAL AND RECURRENT LESIONS ON RECURRENCE RATE OF REGIONAL ENTERITIS

Surgical Treatment	No. Procedures	No. Recurrence	%
Partial exclusion	34	20	59
Complete exclusion	30	17	57
Partial exclusion resection	39	26	67
Complete exclusion resection	45	32	71
Primary resection	240	161	67
Ileostomy	12	6	50
Total	400	[illegible]	

P t t f ll w d tw y

plete obstruction of the bowel resulted in 5–10% of the surgically treated cases Adhesions occurred after all types of surgery but volvulus was more common after resection Diarrhea continued in many cases after surgery

The location and length of the lesion amount of grossly normal small bowel above the lesion removed at surgery sex of patient and type of surgical procedure had no effect on recurrence rate (Table 2) Long duration of disease before surgery youth of patient Hebrew extraction and recurrent disease increased the recurrence rate

[The results of surgery compiled in this extensive survey are sobering and should deter any one from surgical intervention in this disease unless such a course is forced by obstruction, fistulas or rectal complications It may even be questioned whether failure of conservative management to maintain a reasonable state of health is a proper indication for a treatment which in only one of every three cases arrests the disease for two years Since the figure for arrested cases probably includes patients with recurrent but asymptomatic disease the success of surgery may be even worse Although some types of operations were not carried out in great number another disappointing feature is that the favored operation primary resection did not seem to lead to a significantly greater number of arrested cases than other theoretically less desirable operations In contradistinction to ulcerative colitis (p. 562) surgery obviously cannot

fistulas. Of 39 who had abdominal exploration, 43.7% had fistulas. A history of initial intestinal bleeding was recorded in 6%. Ischiorectal abscesses and fistulas occurred in 184 patients; rectovaginal abscesses and fistulas in a few patients. Polyarthritis of rheumatoid type involving particularly the small joints was encountered in 4.5% of the 600 patients and erythema nodosum was found in 5 patients. Recurrent regional enteritis did not differ from the initial disease, and many years often elapsed before serious complications were noted.

TABLE 1.—SUMMARY OF COMMON SYMPTOMS AND SIGNS FOUND IN 600 CASES OF REGIONAL ENTERITIS

SYMPTOM	PATIENTS	% OF 600
Diarrhea	444	74.0
Colic	402	66.9
Loss of weight	377	62.7
Fever	222	36.9
Blood in stool	96	16.0
Abdominal mass	189	31.4

More than one symptom presented by many patients.

Recurrent lesions extended downwards, not up the small bowel.

Nonsurgical treatment included adequate nutrition, vitamins, encouragement, sulfonamides and antibiotics, corticotropin and cortisone, and roentgen therapy, which appeared to help many patients clinically but increased diarrhea, malaise and intestinal obstruction in others. Of 198 patients not treated by surgery, 36 had good results, 26 fair, 14 were still ill, and the others died, were lost to follow up or had surgery elsewhere. In early cases healing of the lesion is possible, and one patient with 60 cm. small bowel involvement initially had a *normal bowel at cholecystectomy nine years* later. Regional enteritis is more common and has a more fulminating course in Hebrews than in others.

Indications for surgery are: failure of conservative management to maintain a reasonable state of health, intestinal obstruction, fistulas involving the sigmoid and bladder, and the anal and rectal complications of stricture and incontinence. Fistulas limited to the small bowel do not necessarily require immediate operation. An ischiorectal abscess should be drained surgically as soon as loculation occurs, but an anal fistula should not be operated on until the abdominal lesion is

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P t t f ll w d tw y

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More than one symptom presented by many patients

Recurrent lesions extended downwards not up the small bowel

Nonsurgical treatment included adequate nutrition vitamins encouragement sulfonamides and antibiotics corticotropin and cortisone and roentgen therapy which appeared to help many patients clinically but increased diarrhea malaise and intestinal obstruction in others Of 198 patients not treated by surgery 36 had good results 26 fair 14 were still ill and the others died were lost to follow up or had surgery elsewhere In early cases healing of the lesion is possible and one patient with 60 cm small bowel involvement initially had a normal bowel at cholecystectomy nine years later Regional enteritis is more common and has a more fulminating course in Hebrews than in others

Indications for surgery are failure of conservative management to maintain a reasonable state of health intestinal obstruction fistulas involving the sigmoid and bladder and the anal and rectal complications of stricture and incontinence Fistulas limited to the small bowel do not necessarily require immediate operation An ischiorectal abscess should be drained surgically as soon as loculation occurs but an anal fistula should not be operated on until the abdominal lesion is

following ingestion of FS or Marcy inoculum could not be attributed to the fecal content of the inocula

In poliomyelitis infectious hepatitis Coxsackie virus infection and gastroenteritis the causative filtrable agents are found in the stool In all doubt exists as to the natural mode of spread Respiratory as well as enteric spread are thought to be important but attempts to transmit gastroenteritis by inhalation of throat washings from infected persons were unsuccessful The fecal oral route rather than the respiratory is most probably concerned in the spread of nonbacterial gastroenteritis

Demonstration of nonbacterial gastroenteritis caused by more than one agent is in keeping with previous epidemiologic observations At least two such nonbacterial agents can be demonstrated in stool supernates and others may exist The two types of gastroenteritis described are separate entities and it is proposed that the terms afebrile and febrile infectious nonbacterial gastroenteritis be adopted until the causative agents have been classified

[Epidemiologic studies such as this establish viral gastroenteritis as a definite clinical entity —Ed]

Role of Atypical Disease in Continuing Mortality of Acute Appendicitis Frederick Fitzherbert Boyce[5] (Tulane Univ) states that mortality of acute appendicitis has fallen decisively in the last 25 years particularly in the last several years The improvement however is still not satisfactory because in 1952 in the United States 2 600 persons died of acute appendicitis (1 7/100 000 population) A major cause of the continued mortality is failure to realize that atypical manifestations are present in 25% or more of all cases Atypical cases are likely to occur in obstructive acute appendicitis at the extremes of life during pregnancy and when the disease is preceded by trauma Of 7 613 cases analyzed the mortality rate was high in patients whose initial symptoms were nausea and vomiting malaise diarrhea or urinary and when the pain location was atypical Atypical initial symptoms include headache backache fever flatulence periods of anorexia chills hematemesis nosebleed melena syncope hiccup and vertigo Diarrhea present in 5% always confused and delayed the diagnosis Fever was lacking in 15% less than two thirds

(5) A I t. M d 40 669 693 Ap l 1954

be relied on to cure regional enteritis The efficacy of corticotropin and cortisone in arresting regional enteritis is debated, but these agents no doubt can produce remissions and would not have to be exceptionally effective it would seem to rival the results of surgery—Ed]

Study of Illness in Group of Cleveland Families VII Transmission of Acute Nonbacterial Gastroenteritis to Volunteers, Evidence for Two Different Etiologic Agents. William S Jordan Jr Irving Gordon and William R Dorrance[4] fed infectious bacteria free stool suspension supernates obtained in family outbreaks of gastroenteritis to

Characteristics of Illnesses Induced by Two Different Gastroenteritis Inoculums

	Inoculum	
	Marcy	FS
Incubation period		
Range *hrs*	24–120	20–30
Average *hrs*	60	27
Duration Average *hrs*	96	24
Fever	Usually absent late with dehydration below 101 F	Usually present often relatively high
Constitutional symptoms	Usually mild	Usually marked
Headache	Mild or absent	Moderate or severe
Nausea and anorexia	Common moderate or severe	Common moderate or severe
Abdominal pain	Hyperactive peristalsis cramps of moderate intensity preceding diarrheal stools	Persistent pain and cramps, often severe associated with desire to vomit or move bowels
Vomiting	Often occurs in bouts early in illness	Often occurs in bouts early in illness
Stools	Frequent, watery	Infrequent normal or loose

healthy human subjects to explore the possibility that two types of gastroenteritis afebrile and febrile occur in families Illness characterized by two different clinical pictures resulted (table) The more intense symptoms of the febrile disease (FS) were brief complete anorexia on one day being followed by return of appetite the next The volunteers preferred the watery diarrhea of the afebrile illness (Marcy) to the headache and abdominal pain of the febrile disease An attack may confer a *short lived immunity* *Cross immunity* was not demonstrated Noninfectious stool supernates fed to serve as controls for toxic or psychosomatic factors did not produce definite illness in any subject implying that definite illness

(4) J Exper Med. 98 465-475 November 1953

dicitis is suspected during pregnancy is to exclude medical conditions then operate without delay for the process tends to spread with alarming rapidity Pyelitis is the condition most likely to cause confusion

Periodic Peritonitis—Heredity and Pathology Report of 72 Cases Periodic peritonitis is a disorder of unknown cause characterized by short episodes of pain in the abdomen and elsewhere fever leukocytosis and regular or irregular recurrences over many years The disease affects persons of Armenian Arabic or Jewish extraction especially Of the 72 patients studied by Hobart A Reimann Jean Moadie Samuel Semerdjian and Philip F Sahyoun[6] (American Univ of Beirut Lebanon) 49 were Armenian and 23 Arab There were 40 males The disorder began before age 12 in 35 of 56 cases The period between attacks was three days to one year In some the intervals between attacks were irregular and in some attacks were absent during pregnancy The commonest complaint of 58 patients was abdominal pain Vomiting occurred in 16 a chill or chilliness in 15 nausea in 14 constipation in 8 and diarrhea in 8 Abdominal distention flatulence sweating headache oliguria frequency and polyuria were noted in a few instances

The disorder was present in relatives in nine instances In one Armenian family 20 members in five generations were affected Pregnancy temporarily suppressed episodes in each instance In some the severity of symptoms gradually lessened with advancing age and in some disappeared spontaneously

The underlying mechanism and the reason for repetitive uniform episodes of the disease are unknown Evidence indicates that it is a hereditary disorder The occurrence in many cases of synchronous stethalgia and arthralgia and in some of a shift of symptoms from the abdomen to the chest or the opposite or to the joints supports the view that other periodic disorders may be of similar nature A sterile mild nonsuppurative inflammatory process involving the walls of the appendix and gallbladder was demonstrated in six patients operated on during or between episodes The symptoms and pathologic findings justify the u e of the term acute peritonitis The pathologic process seemed to originate in the serosa There was slight cellular invasion of the myenteric plexus

(6) J A M A 1 4 1 541 9 Ap 10 19 4

had temperatures between 99 and 101 F Gangrene or rupture of the appendix may occur without fever Acute appendicitis *can exist without localization of tenderness and distention* may be a sign of the disease Rigidity is neither a constant nor an essential sign it is more common in young than in older persons

Of 6835 white blood cell counts the range was 2000-39050/cu mm only 41 5% were within the 10000 15000 range said to be typical of acute appendicitis The blood sedimentation rate is of no help in diagnosis The diagnosis of acute appendicitis may of course easily be missed in the presence of associated disease

Routine use of *antibiotics is not necessary* in simple acute appendicitis and in fact confuses the diagnosis Acute appendicitis develops atypically when antibiotics are used however justifiably for some other condition Appendicitis in childhood often coincides with other diseases including the exanthems upper respiratory disease and pneumonia which may confuse the diagnosis Diarrhea is a particularly confusing symptom in children Urinary symptoms are more frequent in young children because of the position of the bladder The rectal examination is very useful in children because the pelvis is small and the appendix may be within reach of the examining finger

The mortality rate is highest in aging adults because of the rapidity of development of the pathologic process The initial symptoms may include vague digestive distress and/or diarrhea Localization may take days in contrast to hours in younger persons or may not occur at all Physical findings are scanty in older persons a uniform soft distention is common and highly misleading In the older patients the diagnosis was missed in 15% but operation was usually performed fairly promptly because some other acute abdominal state was suspected *Older patients with vague and chronic complaints referable to the abdomen and associated with the digestive process may have appendicitis and should be carefully watched*

Acute appendicitis in pregnancy is infrequent and usually occurs in women who have had previous attacks Symptoms are usually atypical and the pain is apt to be located higher in the abdomen than usual The safest policy if acute appen

Habit constipation may be differentiated from Hirschsprung's disease on the basis of history and physical examination In Hirschsprung's disease the constipation dates from birth the abdomen is distended there is no fecal incontinence and the rectum usually contains no feces In habit constipation the symptoms begin at ages 2 3 years the abdomen is rarely distended the rectum contains large amounts of feces and fecal incontinence may develop Barium enema will permit differentiation in Hirschsprung's disease the rectum and rectosigmoid are narrow and the rest of the colon dilated

Habit constipation is treated by convincing the parents that no serious disease is present and that bowel movements should not be a point of contention between parents and child A low residue diet mineral oil and milk of magnesia for a few weeks are helpful Psychiatric help may be required for the management of fecal incontinence Hirschsprung's disease on the other hand is treated by removal of the defective portion of the colon down to the internal sphincter and restoration of the intestinal continuity by pull through anastomosis Anal continence should be preserved The operation will interfere with neither male potency nor ejaculation

Untoward Effects of Enemas in Congenital Megacolon are described by Mary R Richards and Robert B Hiatt[7] (Columbia Presbyterian Med Center) Syncope frequently follows enemas in patients with congenital megacolon particularly when the solution is water and when one of the parasympathomimetic drugs is given coincidently Wesley stated that children with achalasia of the lower bowel occasionally suffer from collapse while attempting to defecate

CASE 1—Girl 4 received two large colonic lavages and a soapsuds enema The next morning she was unconscious and in convulsions Because of extreme abdominal distention 7 7 L tap water was given by colonic lavage with return of brown fecal material She became cyanotic and convulsive Bloody froth appeared at her mouth and she died within two hours Autopsy disclosed congenital megacolon containing 3 2 L fluid congestion of the leptomeninges flattened convolutions narrowed sulci reduction in size of the lateral ventricles and severe pulmonary edema

CASE 2—Boy 3 had been given 0 5 Gm neostigmine twice daily and enemas as required One day after a soapsuds enema was given and retained neostigmine was given One hour later while straining to defecate he frothed at the mouth lapsed into coma and died.

(7) P d t 12 253 258 S ptemb 1953

which indicates that neuromuscular disturbance may account for the immediate origin of symptoms and signs The few ad hesions and little cicatrization or thickening as residues of hundreds of attacks were remarkable findings

The differential diagnosis of periodic peritonitis and acute abdominal disease such as acute appendicitis is difficult helpful diagnostic features are history preceding similar epi sodes in the patient or his relatives synchronous pain in the chest or joints and urticaria or other dermal eruptions

[Episodes of abdominal pain arthritic symptoms and dermal erup tions at times characterize such parasitic infestations as echinococcosis but in most instances they are ascribed to allergic reactions of unknown etiology The familial and racial incidence and the absence of purpura and urinary abnormalities appear to differentiate the syndrome here described from that described by Osler as visceral manifestations of the erythema group of skin diseases (Am J M Sc 127 1 1904) —Ed]

Classification and Treatment of Children with Severe Chronic Constipation Orvar Swenson[6] (Boston) states that the most common cause of severe chronic constipation in chil dren is faulty habit that often begins when the child starts to walk and explore his surroundings he rebels against taking time out for eliminations His negative attitude is aggravated by overzealous parents who make an issue of bowel move ments with the result that emotional tension develops between the parents and the child Most children will eventually have normal bowel habits but some continue to have symptoms of constipation and may have fecal incontinence Unlike the fecal incontinence of neurologic disease however habit inconti nence occurs without concomitant disturbances in bladder control

Constipation due to disease is rare compared to that caused by poor habits and emotional problems It usually fol lows surgical repair of the imperforate anus but is not accom panied by fecal incontinence Both urinary and anal inconti nence is common in children with myelomeningoceles The rarest of conditions producing severe constipation is Hirsch sprung s disease in which a congenital defect in the pelvic parasympathetic system results in an aganglionic segment of colon that normally is supplied by this portion of the autonom ic system The absence of peristalsis in the involved segment results in the accumulation of fecal material proximally The bladder is often large and somewhat atonic

(6) Am J S g 86 497 499 N mbe 1953

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(6) Am. J Surg 86 497-499 No embe 1953

renal or cardiac disease Barium salts for diagnostic enemas should be suspended in isotonic saline rather than water Potentially toxic substances such as magnesium sulfate and borax should not be used in enema solutions in patients with congenital megacolon Neostigmine orally should be given in smaller doses than those usually recommended

An established attack should be treated with 2% sodium chloride intravenously

Intestinal Parasitosis Caused by Endameba Histolytica (Nondysenteric Intestinal Amebiasis) Carlos Gual Castro and Jose Ma de la Vega[8] reviewing the records of 1 000

CLINICAL PICTURE IN PATIENTS WITH INTESTINAL PARASITOSIS AND THOSE WITH IRRITABLE COLON

S A D S M TOMS	PARAS OS S I	C N
Constipation	48	44
Diarrhea	55	39
Meteorism	65	53
Diffuse pain	33	32
Colicky pain	50	44
Mucus	26	18
Pus	25	15
Bleeding	16	5
Anorexia	15	10
Asthenia	21	14
Loss of weight	18	8

Mexican outpatients found that 338 had intestinal parasitosis caused by E histolytica In 105 of these E histolytica alone was responsible for the condition in 49 this parasite was associated with others and in 184 patients parasitosis was accompanied by various other disorders such as gastroduodenal ulcer cholelithiasis diabetes mellitus and visceral neurosis No evidence of specific ulcerous lesions could be found in any of the patients (except for two who were dropped from the study) The 105 patients with uncomplicated infestation were compared with 100 patients with irritable colon none of whom were infested with E histolytica or had signs of any other disease From the distribution of the signs and symptoms in each group shown in the table it can be seen that there is no characteristic symptom on which to base a positive differential diagnosis

Specific treatment eliminated the parasite in 74% of the

(8) Rev st 1 5 195 207 Ap J 1953

CASE 3—Boy 6 after an injection of 0 045 Gm neostigmine and a soapsuds enema had pain in the throat and vomited He said he could not see Blood pressure was 60/20 mg Hg He was given 0 0001 Gm atropine sulfate and gradually improved

CASE 4—Boy aged 15 months had been treated with neostigmine and enemas He became irritable cyanotic pulseless and coughed and gagged repeatedly during a colonic irrigation Several further lavages were without incident Later a similar episode cleared when lavage was stopped Pulmonary edema occurred on one occasion Another time two doses of neostigmine followed by irrigation caused shock which improved on injection of atropine

CASE 6—Boy 4 received an enema of 1 qt borax in water He became nauseated and vomited then cold and clammy He responded to plasma glucose and saline intravenously and heat

CASE 7—Girl 6 retained most of a tap water enema Three hours later her abdomen was hard and she urinated large quantities frequently One and one half hours later another enema 60 Gm cane sugar and 60 Gm sodium bicarbonate in 200 cc water was given She vomited complained of headache and her skin became clammy Irritability and weakness developed and she lapsed into coma and had tonic convulsions During 2½ hours of coma fecal material and fluid were passed from the anus She recovered complained of thirst and drank eagerly

CASE 8—Girl 6 was in shock after a 700 cc soapsuds enema The abdomen was rigid and tender She recovered spontaneously

CASE 9—Boy 4 fainted occasionally after enemas with soapy water but not when oil enemas were used

The clinical picture characterized initially by weakness headache vomiting and cough and eventually by pallor perspiration polyuria coldness of the skin syncope and sometimes death in coma and convulsions is best explained by water intoxication The pathophysiology is apparently altered function particularly of the central nervous system caused by a sudden increase in intracellular water content Support is lent by the postmortem findings in Case 1 chemical findings in Case 5 and the fact that in most cases water or solutions of low osmotic pressure were used for the enema

Neostigmine intoxication is an additional factor This is similar to water intoxication except for pinpoint pupils blurring vision and dyspnea Coma occurs only terminally Alimentary absorption is normally poor but may be enhanced by stasis and hypertrophy of the colonic mucosa

To prevent such reactions isotonic saline solution can be used in the absence of cardiac or renal disease An inert isotonic solution such as 7% gelatin is preferable when there is

sponse to the initial course of therapy was excellent in 8 good in 14 fair in 6 and poor in 2 The type of response did not correspond to severity of the illness Roentgen changes observed in the colon rarely showed much improvement and were at times progressive even though symptoms were in remission

Relapse occurred in 16 patients Four relapsed within one to six weeks one three times in fairly rapid succession in the others relapse occurred twice Re treatment induced prompt remission in all four but it was maintained in only two In one continuous treatment with small doses of corticotropin was necessary in one corticotropin had to be discontinued because of rash Twelve patients had delayed relapses 12 18 months after initial therapy usually associated with emotional stress or upper respiratory infection Re treatment with corticotropin induced improvement but in five improvement was less prompt and less complete than that obtained initially No serious untoward reactions were observed Although cortisone was used for treating some relapses the authors generally prefer corticotropin

Idiopathic Ulcerative Colitis Giant Ulceration Following Corticotropin (ACTH) and Cortisone Therapy is reported by E C Texter Jr C W Legerton Jr J M Ruffin J A Boyd Jr and A G Smith[1] (Duke Univ) In 15 patients severe or fulminating ulcerative colitis was treated with corticotropin and in some with cortisone as well Eight patients had sustained improvement and seven had only temporary improvement or became worse

Perforation of the colon developed in one patient and large undermined ulcers in four who subsequently had colectomy The colectomy specimens showed longitudinal ulcers penetrating to the submucosa and extending from a few centimeters to half the length of the colon The mucosa away from the taenia was involved more often than the mucosa overlying the taenia The serosa and muscularis were involved in some areas The muco a between large ulcers appeared relatively normal in some places and in others pinpoint ulcers were observed Fibrosis and other signs of healing were absent Shortening of the colon and other indications of long existing disease were not seen although the disease had been present

(1) A M A A h I t M d 91 744 757 J 1953

patients with parasitosis Eradication of the parasites how ever was not always followed by relief despite specific treat ment and concomitant symptomatic therapy 38% of the pa tients in whom stools were rendered negative still had their initial symptoms On the other hand 37% of the patients in whom specific treatment failed to eliminate the parasites were asymptomatic at the close of the study Among the pa tients with an irritable colon symptoms of intestinal disturb ance persisted in 42% Obviously the mere presence of E histolytica in the intestine is not related to any well defined or characteristic clinical picture in patients without ulcerative lesions and cannot be considered directly responsible for the subjective symptoms The value of specific therapy in such cases is therefore merely prophylactic and at times indirectly psychotherapeutic

[The clinical significance of cysts of E histolytica in the stools is put in proper perspective by this controlled study It should discourage the all too common practice of assuming without further ado that the discovery of a parasite in the stool explains why the patient has head ache epigastric pressure after meals or chronic spasm of the sigmoid —Ed]

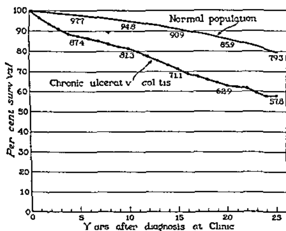
Long Term Results in Corticotropin Treated Ulcerative Colitis are discussed by C Wilmer Wirts Martin E Rehfuss and Herbert A Yantes[9] (Jefferson Med College) Of 26 men and 14 women 7 were acutely 18 severely 14 moderately and 1 mildly ill Five were having their first attack one had had the disease 25 years and the others 3 5 years Most had had relapses every one to two years Initial treatment was 20 or 25 mg corticotropin intramuscularly every 6 12 hours for a week and reduced dosage for 2 more weeks as clinical improvement occurred Some received 20 mg corticotropin in 500 cc of 5% dextrose in water continuously for eight hours daily for one to two weeks followed by reduced dosage either intravenously or intramuscularly for one week This was most effective and usually resulted in a fall of fever reduced stools improved appetite and increased sense of well being The medication was rarely given longer than three weeks All received bed rest sedatives fluids parenterally blood transfusions antibiotics and a high caloric high protein diet

Of the 40 patients 15 were followed over 2½ years 10 over 2 years 10 over 1½ years and 5 less than 1 year Re

(9) J A M A 154 36 39 Jan. 2 1954

complications such as giant ulceration perforation and hemorrhage (2) the problem of exacerbation on withdrawal of the hormones and (3) the possibility that corticotropin and cortisone become somewhat less effective on repeated use These disadvantages however appear to be outweighed by the beneficial effects possible dramatic remissions are achieved in many cases particularly if therapy is initiated with corticotropin given intravenously or intramuscularly in large doses Small maintenance doses of cortisone may be used if necessary to keep patients in remission without the fear of serious side effects Finally the use of these agents if unsuccessful does not seem to contraindicate surgical treatment which has made remarkable progress As described in the next report the results of primary resection of the diseased colon are so superior to the results of preliminary ileostomy followed by resection that there would appear to be few reasons for carrying out the latter procedure —Ed]

Development of Cancer in Chronic Ulcerative Colitis J Arnold Bargen William G Sauer Wyman P Sloan and Robert R Gage[3] (Mayo Clinic and Found) report 25 year



F g 93 —S l curv f p t t w th h l t col t (C rt y f B g J A r l G t oe t l gy 26 3 3 J y 1954)

survival in 57 8% of 1 564 patients under 50 at the time of diagnosis of chronic ulcerative colitis seen initially between Jan 1 1918 and Dec 31 1937 as against a survival rate of 79 3% among the normal population (Fig 93) None of the patients had malignant lesions within one year of diagnosis Fatal malignant rectal and colonic lesions developed subsequently in 98 patients Expected deaths due to malignant neo

(3) G t t l gy 6 3 37 J y 1954

for about a year in each of the patients The deep undermined ulcers and absence of fibrosis may be related to the use of corticotropin and cortisone The ulcers are similar to those occasionally seen in fulminating severe ulcerative colitis They are unusual however because of the similarity of the lesions in each case and because they developed within a short period after corticotropin and cortisone was discontinued

Subsequently another patient treated with corticotropin had huge linear ulcers one of which perforated transecting the entire length of the transverse colon

Primary Resection of Colon in Acute Ulcerative Colitis Charles B Ripstein[2] (State Univ of New York Brooklyn) states that primary resection of the diseased colon with ileostomy is the operation of choice in cases of acute ulcerative colitis that fail to respond to medical therapy Results with simple ileostomy have been poor with a mortality of 20-60% due to severe blood and protein loss from the retained bowel and infection In Ripstein s experience about 60% of patients have responded to medical treatment with transfusions antibiotics corticotropin banthine* and psychotherapy He considers resection of the colon indicated if medical therapy does not produce a remission within three weeks if there is actual or impending perforation if bleeding continues and if there is septicemia or metastatic infection such as endocarditis pyoderma or arthritis

During surgery frozen section biopsy should be done on the terminal ileum to make sure that the exteriorized bowel is microscopically free from disease A small segment of rectum is left in place to minimize shock but is removed three to six months after the initial operation as carcinoma may develop

One stage resection of the colon was carried out on 43 patients All had severe diarrhea and fever six had massive hemorrhage eight perforation three metastatic infection and two carcinoma *of the colon* Two *died of ulcerative* endocarditis and septicemia All others recovered although one later died of carcinoma of the bowel There were no deaths from ulcerative colitis

[The status of corticotropin and cortisone in the treatment of ulcerative colitis is becoming more crystallized Disadvantages are (1) serious

(2) J A M A 152 1093 1095 J ly 18 1953

Procedure —All subjects were on unrestricted diets One half received various quantities of human blood by gastric tube or by mouth The other half ingested commercial iron preparations at a dosage providing 180 mg reduced iron a day All stools for the next 64 72 hours were tested by (1) the guaiac test and (2) Gregersen s modification of the benzidine test (1) To a small piece of feces on filter paper are added 2 drops each of glacial acetic acid 95% ethanol solution of gum guaiac and 3% hydrogen peroxide in that order Color is read in five minutes and graded 0-4 + (2) A mixture of 0 025 Gm. benzidine base and 0 20 Gm barium peroxide is dissolved in 5 ml of 50% acetic acid and 2 drops of this is added to feces smeared on filter paper The result is read in 15 30 seconds and graded 0-4 +

A significant number of persons with blood loss in the stomach of 50 ml on a single occasion was not identified by the guaiac technic 70% of stool samples giving a 0 or 1 + reaction A higher percentage of negative results was obtained with 25 ml blood loss It appears that the critical level of single blood loss guaiac sensitivity lies between 25 and 50 ml The benzidine test showed values over 1 + in 48% of samples after 25 ml blood loss and in 66 after 50 ml

Eleven normal subjects were fed 15 ml packed red cells daily for four to seven days In a majority the guaiac test failed to give more than a 1 + result In one subject every stool was negative The benzidine test gave 3 + to 4 + reactions in at least two stools for each subject A single random stool might have a negative reaction in either method but the probability that two or more successive stools would be negative in the benzidine test is very low

It is usually claimed that the benzidine test is too sensitive giving false positive results in subjects on ordinary diets *However of the controls on normal diets with iron supple* ments 22% had 1 + 6% 2 + and 4% 3 + reactions in the benzidine test Thus 10% of the control stools showed 2 + or 3 + reactions whereas 2% of the stools tested with guaiac showed similar results The reputation for oversensitivity of the benzidine test does not apply to the modified Gregersen procedure which has only one fifth the sensitivity of the unmodified procedure employing hydrogen peroxide

plasm of the rectum and colon among a group of similar size and age drawn from the general population number three or four The death rate from rectal or colonic cancer among patients with ulcerative colitis is about 30 times that among the general population of the same age and sex (table) Cancer threatens the younger patient with chronic ulcerative colitis more than the older patient

Since annual deaths from cancer of the colon or rectum

CHRONIC ULCERATIVE COLITIS COMPARISON OF OBSERVED DEATHS FROM MALIGNANT NEOPLASM OF COLON WITH EXPECTED DEATHS IN GENERAL POPULATION

OSI	TIENTS	P BO EA EXPOSED	XPECTED TH		VE EATH ( ) MALI ANCY OF TH ECTUM AND COLO	RATI OF TO EXPECTE	IE VED TH
			T tal malignant neoplasms E_1	M lignant eoplasms of d ges rga and peri toneum E_2		$O{-}E_1$	$O{-}E_2$
2–4	8	132 5	0 010	0 001	1		
5–9	25	304	0 023	0 00	5	85 5	650 0
10–14	65	863 5	0 117	0 017	7		
15–19	127	1 424 5	0 280	0 050	12	42 9	240 0
20–24	219	2 609 5	0 938	0 208	11	11 7	52 9
25–29	294	3 945 5	2 845	0 67	17	6 0	22 2
30–34	301	3 911 5	4 478	1 342	15	3 3	11 2
35–39	229	3 151 5	5 746	1 930	9	1 6	4 1
40–44	166	2 144 5	5 702	2 107	15	2 6	7 1
45–49	130	1 738 5	6 631	2 676	6	0 9	2 2
Total	1 564	20 225 5	26 772	9 100	98	3 7	10 8

E pect t ons alcul ted from d th tes U S 1949 in V tal Statistics

among patients with ulcerative colitis number 1 2/100 and since the average colitis patient aged 31 has better than a 50% chance of living 25 years early removal of the colon does not appear advisable

Selection of Screening Procedure for Detecting Occult Blood in Feces **Albert I Mendeloff**[4] (Washington Univ) states that the purpose of testing for occult blood in feces is to determine whether there has or has not been bleeding of a certain magnitude into the intestines To judge this one must know what is the greatest quantity of blood lost into the upper gastrointestinal tract either at a single hemorrhage or at a constant daily rate which would consistently escape detection by the commonly used tests even if every stool passed were tested

(4) J A M A 152 798 801 J 27 1953

METABOLISM



PHILIP K. BONDY M.D.

PART VI

METABOLISM

THE THYROID GLAND

Influence of Estrogen on Thyroid Function. William W Engstrom and Blanch Markardt[1] (Milwaukee) gave 75 100 mg diethylstilbestrol daily to 12 men aged 45 74 and 25 30 mg daily to 5 women aged 21 70 2 women aged 18 and 30 received 5 mg premarin® daily Most patients were chronically ill with carcinoma of the prostate or breast or had osteoporo sis A control serum precipitable iodine (SPI) determination was obtained for all patients and the course of the SPI level followed at different intervals after therapy was begun The patients were followed clinically for evidences of hyperthy roidism and in some resting pulse rate and BMR were fol lowed Estrogen therapy was discontinued in 10 patients and the SPI level followed

In 12 men and 7 women the SPI level rose in all instances during estrogen administration With few exceptions the in crements were generally linear at least up to three weeks During this interval the mean SPI level had increased from 4 6 to 6 6 μg % and in general patients with the higher con trol values tended to have the highest SPI levels with estro gen therapy Patients who received estrogen for longer periods had a leveling off in the increments by the third or fourth week In women estrogen equivalent to 25 mg diethylstil bestrol produced as much of a rise in SPI level as 100 mg in men The SPI level gradually fell toward the normal control range in all instances when estrogen was discontinued

Despite progressive increments in SPI neither the rest ing pulse rate nor the BMR was significantly altered and hyperthyroidism was not found clinically An effort was made to determine whether the increments of SPI were due to an actual increase in thyroid activity or to an alteration in the mechanism of disposal of circulating hormone Patients with

(1) J Cl E doc 1 14 215 222 F b ry 1954

had or had not received TSH In experiments in which propyl thiouracil was administered (I and III) the thyroidal content of organically bound I[131] was negligible

In experiment I the mean thyroid/plasma iodide concentration ratios in groups not given TSH varied from 6 2 to 12 3 as against 142 to 150 in groups that did Cortisone did not significantly affect concentration ratios in either group

In experiment II the rate of disappearance of I[131] from the plasma of animals given cortisone greatly exceeded that in animals not so treated and was further augmented by administration of TSH Calculated values for total plasma iodide clearance were similarly altered The mean thyroidal iodide clearance was not affected by cortisone whether or not the animal received TSH

In experiment III the rate of disappearance of iodide from the plasma was greatly increased by cortisone being 20 3%/hour in animals given cortisone alone and 14 1% in animals also given TSH The more rapid disappearance of I[131] from the blood of animals given cortisone could be explained by the significant increase in renal clearance of iodide in these animals The mean renal clearance of iodide was 5 1 cc /hour in animals not treated and 4 2 cc /hour in those given TSH alone The mean clearance was 17 8 cc /hour in animals given only cortisone and 15 5 cc in those given TSH in addition to cortisone

[The relationship between adrenal and thyroid function is still debatable and this study emphasizes the difficulty of drawing conclusions from such nonspecific single functions as radioiodine uptakes —Ed]

Physiologic Activity of 1 Triiodothyronine was investigated by J Lerman[3] (Massachusetts Gen l Hosp) In four patients with myxedema 0 1 mg of the drug was administered intravenously and BMR changes noted and compared with the effects of thyroxin polypeptide or 1 thyroxin In one patient at the start of the metabolic assay the effect of a single dose of 0 1 mg 1 triiodothyronine on serum protein bound iodine (PBI) concentration and on urinary excretion of iodine was compared with the effect of 0 42 mg dl thyroxin In a fifth patient for whom no basal metabolic assay was made the effect of 0 2 mg 1 triiodothyronine was compared with that of 0 2 mg 1 thyroxin on the PBI level and on urinary excretion of iodine

(3) J Clin Endoc 1 13 1341 1346 N mb 1953

anterior pituitary deficiency or myxedema secondary to previous thyroidectomy who were maintained on constant amounts of exogenous thyroid, were given diethylstilbestrol Presumably the thyroid glands of these patients could not appreciably increase their activity Of seven such patients five had no change in SPI level

This study indicates that the increments in SPI are due to an increase in thyroid activity at least for a time and are not due to an altered rate of disposal of thyroid hormone Increased elaboration of estrogen may be an important factor in the increased concentrations of SPI seen in normal pregnancy Administration of large amounts of estrogen appears to confer some increase in tolerance to increased amounts of circulating thyroid hormone The underlying mechanism whereby the function of the thyroid is altered by estrogen is not entirely clear

[These observations are helpful in understanding the normal rise of SPI levels in pregnancy —Ed]

Effect of Cortisone on Thyroidal and Renal Metabolism of Iodine was investigated by Sidney H Ingbar[2] (Boston City Hosp)

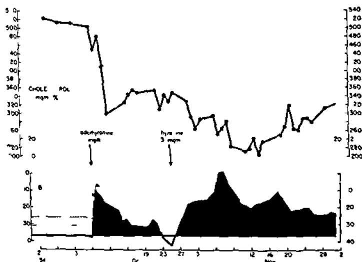
Method —Male albino rats 10 days after hypophysectomy were used In experiment I 35 rats divided into six groups received propylthiouracil Groups A B and C received a total of 1 0 mg TSH (pituitary thyrotropin) groups D E and F received none A and D group animals received a total 12 5 mg cortisone B and E group animals received a total 6 25 mg cortisone groups C and F received none Animals were killed 60 90 minutes after receiving I^{131} In experiment II 64 animals divided into four groups received no propylthiouracil Animals in groups A and B received a total 1 5 mg TSH groups C and D received none A total 20 mg cortisone was given to groups A and C groups B and D received none Each group was in turn subdivided into four time subgroups killed two four six and eight hours after receiving I^{131} In experiment III 80 animals all given propylthiouracil were divided into four group Group A or B received a total 1 0 mg TSH and group C and D received none Groups A and C received a total 25 mg cortisone and groups B and D received none Each group was in turn subdivided into four time groups killed two four six and eight hours after receiving I^{131} Urine was collected at two hour interval after administration of I^{131}

In no experiment did cortisone significantly influence the ratio of thyroidal mass to body weight whether the animal

( ) End 1 gy 171 131 Aug 19 3

mental data suggest that triiodothyronine leaves the extra cellular spaces rapidly to enter tissue cells thus accounting for rapid BMR rise The precipitous drop in BMR after omission of the drug suggests that it disappears rapidly from intra cellular fluid A high iodine content in the urine of one patient after a single dose of the drug tends to confirm this view It is suggested but not proved that thyroxin serves as a reservoir for triiodothyronine and that the latter converted from thyroxin in the tissue cells is the effective thyroid hormone

l Triiodothyronine Versus l Thyroxin Comparison of Their Metabolic Effects in Human Myxedema Rulon W Rawson J E Rall O H Pearson Jacob Robbins Helen F Poppell and C D West[4] (Cornell Univ) studied the metabolic effects of diiodothyronine triiodothyronine and thyroxin in a woman 41 with classic Gull s disease The control BMR was between — 44 and — 32% Diiodothyronine 1 mg caused no change in the pulse or BMR Triiodothyronine 1 mg intra



F g 95 —Eff ct f l t od thy d l thyro on BMR d on serum h le te l BMR l es plotted f llow g inj cti f tr odothyr nine rep se t th ee p t ru g g f th b erved lu S l d l befor inject n f t od hy p se t a e g p et eatm t BMR B ok n l e p ts g BMR bta ed t 11 m d dott d l rag BMR 4 p m (Court sy f R w R W et l Am J M Sc 2 6 405-411 Oct be 1953)

(4) Am. J M S 226 405 411 O t be 1953

Results of the assay of l triiodothyronine on the four patients with myxedema are shown in Figure 94. Clinical effects and changes in blood cholesterol concentrations produced by l triiodothyronine were comparable with those produced by thyroxin. Administration of l triiodothyronine caused little or no change in PBI level for 24 hours, whereas doses of thyroxin of lesser physiologic activity but of equal or greater weight produced an appreciable rise. Iodine in the

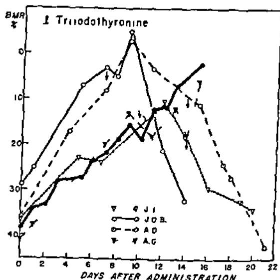


Fig 94.—Calorigenic response of four patients with myxedema to daily administration of 0.1 mg l triiodothyronine intravenously. Solid black line represents standard curve of response to administration of dl thyroxin polypeptide in 0.5 mg iodine daily. Small arrows indicate day of final dose. (Courtesy of Lerman, J.: J Clin. Endocrinol 13: 1341-1346, November, 1953.)

urine did not explain the variations in the blood iodine concentrations. In three of the patients in whom an assay was made (Fig 94), the BMR reached the pretreatment level in from seven to nine days after omission of the hormone. This is in marked contrast to the change in metabolism observed when a hypothyroid patient treated with thyroid or thyroxin stops medication. The slow drop in metabolism over 50-70 days represents the "decay curve" of thyroxin as described by Means and Lerman and by Thompson *et al.*

l Triiodothyronine is more active than l thyroxin. Experi-

differences on nitrogen and phosphorus excretion were in the speed with which these metabolic effects occurred

In all metabolic effects triiodothyronine was effective almost immediately whereas thyroxin was slow and prolonged No qualitative differences in effects of these compounds were noted The serum protein bound iodine level following administration of triiodothyronine rose promptly and practically disappeared after 36 hours after 1 thyroxin it rose considerably higher and fell almost to pretreatment levels in 18 days (Fig 96) This might be a reason for the differences in speed of action Triiodothyronine and thyroxin labeled with I^{131} had a half life of 2½ and 6-12 days respectively Following administration of thyroxin radioactivity persisted over the liver for some time Radioactivity disappeared promptly following administration of triiodothyronine

[From these studies and from that of Asper Selenkow and Plamondon (1953 54 YEAR BOOK p 603) it is clear that triiodothyronine acts rapidly in a manner qualitatively similar to thyroxin Although there is some doubt as to the relative potencies of the two hormones given in single doses (viz Rawson *et al*) the maintenance dose of thyroxin appears to be about five times that of triiodothyronine —Ed]

Penethamate Hydriodide (Neo Penil®) Influence on Blood Protein Bound Iodine Levels Spurious elevation of blood protein bound iodine levels (not due to hyperthyroidism) is caused by a variety of medications and diagnostic procedures Arthur Krosnick Hyman I Segal and Harold L Israel[5] (Univ of Pennsylvania) found that neo penil® an iodinated ester of penicillin will cause a temporary elevation The effect is transitory even after prolonged administration of large doses in contrast to the elevations produced by iodine containing compounds used for roentgen studies which may last for months or years

In two normal subjects single doses of 500 000 units of neo penil® elevated the protein bound iodine concentrations to the hyperthyroid range 24 hours after the drug was administered The levels returned to the normal range within 48 hours Protein bound iodine levels greater than 30 μg/100 cc blood were found in two patients with lung abscess given 2 000 000 units of neo penil® daily for 4 19 days Levels determined one week after the drug was stopped were within normal range Administration of this drug will temporarily

(5) J Cl E doc 1 14 24 43 F bru y 1954

venously given at 9 a m raised the BMR by 4 p m from an average of —27 to —13% the next morning it was —10% There was rapid return to pretreatment level in 9 days with maximal fall in 16 days (Fig 95) 1 Thyroxin 3 mg intravenously did not produce any changes by 4 p m Next morning the BMR was —26% The fasting BMR rose within eight days to the level observed 24 hours after triiodothyronine The maximum level was at 11 days Twenty six days later it still had not returned to the pretreatment level

The response to thyroxin was between three and four times greater than that to triiodothyronine The latter exerted its

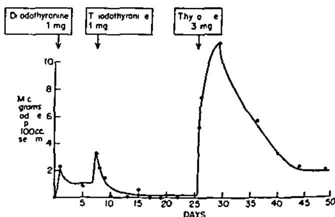


Fig 96—S m p t n bou d d e l 1 f llow g adm st t o f 1-d odothy o l tr d thy a d l thy o (Co te y of R w n R W et al Am J M S 226 405 411 O t b 1953)

action promptly whereas thyroxin had a slow and prolonged effect There was a fall in the serum cholesterol values with both drugs Diiodothyronine had no effect on nitrogen balance Triiodothyronine produced a prompt increase in urinary nitrogen and phosphorus Thyroxin 3 mg had approximately the same effect as 1 mg triiodothyronine on total urinary nitrogen Thyroxin and triiodothyronine had no significant effect on excretion of calcium and no effect on excretion of sodium chloride or potassium Excretion of uric acid and creatinine was not affected by either drug 1 Thyroxin 3 mg exerted between three and four times the effect of 1 mg triiodothyronine on the total BMR The major and significant

them into the fundulus (common Atlantic minnow) The amount of thyroid stimulating hormone (TSH) of these extracts was measured in chicks by the increase in thyroid weight depletion of iodine from the thyroid or by the increase in mean cell height of the thyroid A few fractions which contained appreciable amounts of TSH were found to produce relatively little exophthalmos conversely a few preparations which contained relatively little TSH produced obvious exophthalmos

Analysis of the various procedures whereby these extracts were obtained led to separation of TSH and EPS in appropriate pituitary extracts The study indicates that EPS and TSH are not the same substance and that they can be separated from one another

Failure of Short Term Administration of Thyrotropic Hormone to Produce Exophthalmos in Man The belief that thyrotropic hormone (TSH) is the cause of exophthalmos is based only on animal experiments Benjamin Simkin and Paul Starr[8] (Univ of Southern California) tested this concept in human beings by administering 25 or 30 mg TSH intramuscularly daily to five patients with intact thyroid glands and eight athyrotic patients Serial exophthalmometer readings *showed that after 3 22 days of TSH stimulation changes were* no greater than those of controls

[Although in this experiment its duration and dose of TSH produced definite thyroid effects it is possible that in human beings the thyroid may be more sensitive than the eyes so that some exophthalmogenic effect might have been produced with larger doses or more prolonged treatment —Ed.]

Hyperophthalmopathic Graves' Disease Clinical Observations in 19 Cases followed for 1½ 20 years are presented by Thomas R Hedges Jr and Edward Rose[9] (Univ of Pennsylvania) The patients were divided into four groups (table) according to the state of thyroid function when exophthalmos was first noted There was no apparent relation between severity of ophthalmopathy and level of thyroid function At onset proptosis was symmetrical in 10 patients and asymmetrical in 9 Congestive signs were present without corneal damage in seven patients and with corneal damage in four Eight had no congestive signs at any time Limitation of ocular move

(8) P oc Soc E p B l & M d 84 99 100 O t be 1953
(9) A M A A h Oph h 50 479 490 Oct b 1953

invalidate the use of blood protein bound iodine determinations as a test of thyroid function

Diagnosis of Thyrotoxicosis by Simple Outpatient Radioactive Iodine Technic Alastair G Macgregor H Miller P J Blaney and W S Whimster[6] used the radioactivity of the protein bound fraction of the plasma 48 hours after administration of a tracer dose of 25 30 μc I^{131} as a diagnostic aid in 50 patients studied in Nottingham General Hospital 40 miles from the Sheffield center containing the electronic apparatus the isotope doses and plasma samples were dispatched by train

Activity levels exceeding 0 4%/L in the protein bound fraction were considered indicative of definite thyrotoxicosis whereas values below 0 2%/L were interpreted as excluding it Values between 0 2 and 0 4% were interpreted according to the proportion of whole plasma activity that was protein bound proportions over 50% usually indicating thyrotoxicosis even if the absolute amount in the protein bound fraction was below 0 4%

Adequate follow up of six definitely thyrotoxic patients tested indicated that toxicity and 48 hour protein bound plasma activity lay in the range of 0 7 2 8%/L. Activity levels in 21 of 22 normal persons were 0 1% or less and in 13 of them with the dose given no appreciable activity was detectable One patient had a level of 0 2% Of 22 doubtful cases 15 believed thyrotoxic clinically proved to be so after the radioiodine test and subsequent follow up The initial clinical impression of nontoxicity in four patients was refuted by results of the radioiodine test subsequently found to be accurate In three patients test results were at variance with the final clinical opinion

[This technic makes radioiodine diagnostic methods available to small communities where it would be uneconomical to install the necessary equipment There are important limitations to diagnosis by plasma radioactivity however (see Blom and Terpstra p 591) —Ed]

Thyroid Stimulating Hormone of Anterior Pituitary as Distinct from Exophthalmos-Producing Substance Brown M Dobyns and Sanford L Steelman[7] (Western Reserve Univ) measured the amount of exophthalmos producing substance (EPS) in various anterior pituitary extracts by injecting

(6) Brit M J 2 21 22 J ly 4 1953
(7) E docrinol gy 5 705 711 J 1953

regression in congestive signs may explain this apparent im provement

The study does not justify division of the hyperophthalmo pathic syndrome into the so called thyrotropic and thyrotoxic forms despite the undoubted occurrence of wide clinical vari ations Nevertheless subtotal thyroidectomy or suppression of thyroid function by other means should be avoided in the presence of severe or progressive ophthalmopathy Evalua tion of therapy is hampered by the tendency to spontaneous remissions and exacerbations and by lack of control studies

Hypercalcemia in Thyrotoxicosis may simulate hyperpara thyroidism as demonstrated in three cases reported by Ed ward Rose and Russell S Boles Jr [1] (Univ of Pennsylvania)

CASE 1—Woman 53 was hospitalized with mu cular weakness irregular fever and persistent nausea and vomiting Tentative diagnosis of hyperparathyroidi m could not be confirmed at op eration in July 1949 Immediate postoperative course was stormy The serum calcium content was 15 3 mg /100 cc the second day Admini tration of Lugol s solution for five days resulted in prompt improvement three days after its discontinuance serum calcium content was 12 3 mg /100 cc and about six weeks later was 10 6 mg The serum protein bound iodine level 21 days after cessa tion of Lugol s solution was 8 9 gammas/100 cc On September 13 (39 days after Lugol s solution was stopped) a tracer study showed a 24 hour uptake of 40% and 48 hour uptake of 37% On September 22 after a therapeutic dose of 8 mc I^{131} orally 24 hour thyroid uptake was 29% and 48 hour uptake was 27% In November the serum calcium content was 11 1 mg and inorganic serum phosphorus 3 5 mg /100 cc A tracer study showed thyroid uptake of 27% in 24 hours and 13% in 48 hours

In February 1951 serum calcium content was 9 9 mg /100 cc inorganic serum phosphorus 3 9 mg and thyroid uptake of a tracer dose of I^{131} was 34% in 24 hours and 32% in 48 hours X rays of the skeleton showed some generalized decalcification On October 16 serum calcium content was 9 6 mg /100 cc and the 48 hour thyroid uptake was 37% of a tracer dose of I^{131}

CASE 2—Woman 41 was cachectic and dehydrated when hospi talized in July 1951 and remained a diagnostic problem She was discharged in August and re admitted in November critically ill with prostration dehydration and fever The thyroid was enlarged to about twice normal Serum calcium content determined after rehydration was 13 1 mg /100 cc Alkaline phosphatase level was 3 7 Bodansky units A tracer study revealed a 24 hour thyroid up take of 50% Serum protein bound iodine level was 11 9 gammas/100 cc Propylthiouracil 300 mg daily was given for 41 days during

(1) M Cl N th Am ca 37 1715 1724 N mbe 1953

ments was noted at the first examination in 11 and 6 of these had residual extraocular muscle weakness when the ophthalmopathy became stationary Seven patients had some loss of visual acuity

In 16 patients exophthalmos attained its maximum in 4 1? months after which inflammatory congestive and sympathicotonic manifestations tended to regress and proptosis either remained stationary or gradually receded In eight patients recession varying from 3 to 7 mm occurred in one to six years In patients with significant recession of exophthalmos such recession began one to three years after maximal exoph

THYROID STATUS OF 19 PATIENTS WITH HYPEROPHTHALMOPATHIC GRAVES DISEASE

G p	N f P ie t	Se M	Se F	Ag R Y	G Nod l	G Diff se	
I Mod t se thy t leos (B M R b + r̄	11	4	7	9-68	2	6	3
II Mild h leosis (B M R. les b + r̄)	3	1	2	33-53	1	2	0
III E l (rm l b l met b l				33-45	0		
IV Hyp t d		1		36	0	0	1
T t	9	8	11		3		4

thalmometer readings were noted No patient had a return to so called normal levels In 11 patients no significant recession from maximum levels occurred during 2 12 years Appearance improved in most instances despite persistence of maximal proptosis

There was no significant difference in the course of exophthalmos in patients with high and in those with normal or low metabolic rates Likewise there was no apparent correlation between the course of ophthalmopathy and control of thyrotoxicosis

Treatment of 11 patients with thyrotoxicosis with thiouracil compounds or partial thyroidectomy caused no significant exacerbation of the ocular syndrome In nine patients treated with desiccated thyroid and diethylstilbestrol over long periods there was no correlation between treatment and the course of ophthalmopathy Of 18 patients treated by pituitary irradiation there was a significant recession in exophthalmos in only 2 both received desiccated thyroid over prolonged periods Seven of these patients had gradual decrease in congestive ocular signs within four to six months Spontaneous

number of complications There was a greater percentage of successes among patients with obvious thyrotoxicosis than among those in whom the diagnosis was a little in doubt Thyroidectomy performed for reasons other than toxicity e g thyroid swelling or cosmetic or mechanical reasons produced indifferent results The complications of thyroid surgery in this series were much more common than might be expected

[The optimistic statistics reported from centers specializing in thyroid surgery probably do not reflect the results obtained by general surgeons who perform most of the thyroidectomies One wonders whether this humble and honest report reflects the common experience in hospitals where thyroid surgery is not a particular specialty—Ed]

Prognosis of Hyperthyroidism Treated by Antithyroid Drugs David H Solomon John C Beck Willard P Vander Laan and E B Astwood[3] (Boston) report that of 101 hyperthyroid patients observed for 4 years after completion of a course of therapy with one or more antithyroid drugs—thiouracil 6 ethylthiouracil 6 propylthiouracil and thiobarbital —23 7% had a relapse within 3 months 20 8% had recurrences *3 48 months* later and *55 5% remained euthyroid* Second and third courses of treatment yielded lower remission rates than the first but increased the total number of persons with prolonged remission to 70 3% of the series The frequency of recurrences decreased gradually as duration of remission increased Clinical criteria were used for the most part in assessing the status of thyroid function during therapy and at subsequent examinations

Of the many clinical characteristics analyzed for their effect on the probability of a prolonged remission only a decrease in goiter size during treatment was found to improve the ultimate result significantly When an initially enlarged thyroid decreased unequivocally in size while the patient was receiving the drug the incidence of prolonged remission was 67% and when the thyroid remained constant or increased in size the rate was 31% When the thyroid was normal in size at the end of treatment regardless of initial size the frequency of prolonged remission was 62% in contrast to 39% when a goiter was present at that time The thyroid was normal in size four years after conclusion of treatment in 75 5% of patients in remission at that time Evidence suggests that hyperplasia of the thyroid disappears when a prolonged re

(3) J A M A. 152 201 205 My 16 1953

which time calcium values varied from 11 2 to 19 2 mg /100 cc and serum inorganic phosphorus from 5 2 to 5 7 mg She improved and a subtotal thyroidectomy was performed in January 1952 In September there was recurrence of thyroid enlargement with thyrotoxic symptoms Serum calcium content was 10 9 mg /100 cc and the 24 hour thyroid uptake of I^{131} was 72% She received a therapeutic dose of 7 mc I^{131} and appeared to be in remission when examined in December 1952

CASE 3 —Woman 58 was hospitalized with dehydration weight loss vomiting and muscular weakness Serum calcium content was 14 1 mg /100 cc BMR + 51% and serum protein bound iodine level 13 2 µg /100 cc The 24 hour thyroid uptake of a tracer dose of I^{131} was 63% the 48 hour 49% She improved on 45 mg methimazole daily Serum calcium content varied from 14 1 to 16 9 mg / 100 cc Urinary excretion of calcium on low calcium intake averaged 192 mg /24 hours Because of leukopenia methimazole was discontinued after 21 days She also received potassium iodide and propylthiouracil When discharged serum calcium content was 11 9 mg /100 cc During the next seven weeks she was given propylthiouracil Serum calcium was 13 2 mg /100 cc Two months later thyroidectomy was performed serum calcium content 10 6 mg /100 cc before operation was 11 4 mg one week after operation In the following eight months serum calcium content varied from 10 6 to 11 mg /100 cc and inorganic phosphorus from 3 3 4 mg

Thyroidectomy Follow up Oswald B Tofler[2] reports on 251 thyroid gland operations performed during 1940-48 by various surgeons at Royal Newcastle Hospital Within the first 24 hours there was a 2% mortality The 171 patients followed fell into several classifications Group I or the toxic group was divided into those with (a) undoubted thyrotoxicosis and (b) those in whom there was doubt as to thyrotoxicosis (i e an anxiety state could not be excluded) In group Ia 31 of 44 patients were much better but in group Ib only 16 of 65 could be so classified The condition was unchanged in 5 in group Ia and in 24 in group Ib Group II designated as mechanical consisted of patients complaining of choking feelings and of becoming much worse lately Only 11 of 26 had good results In group IIIa thyroid swelling was the indication for operation 16 of 24 patients failed to derive any benefit Group IIIb consisted of patients operated on for cosmetic reasons

The complications of operation in the entire series were cord paralysis 19 patients voice changes 55 and thyroid deficiency 48 The patients in the toxic group had the greatest

(2) M J A st 1 2 176-178 A g 1 1953

40 age group Sex has little significance in the determination of a remission Patients with a BMR over + 60% did not respond well to thiouracil Duration of the disease did not influence the response There was a higher remission rate in patients whose course of thiouracil was continued for at least nine months—the minimum duration of treatment

After the first course 20 relapses (74%) occurred within six months and 22 (80%) within the first year After the second course six of seven relapses occurred within the first year Patients with toxic nodular goiters should be prepared for thyroidectomy The results with thiouracil were better in patients with small to moderately enlarged goiters The effect of thiouracil on exophthalmos varies between marked increase to complete regression In 6 of 10 cases there was a reversal to sinus rhythm following auricular fibrillation on thouracil alone Five patients had leukopenia but thiouracil was con tinued without ill effect No blood changes were observed fol lowing use of the propyl derivative

[These results may be compared with those in Tofler s group Ia (p 580) or with the 8/‴ surgical cure rate reported by VanderLaan and Swenson (New England J Med 236 ͜36 1947) —Ed]

Evaluation of Antithyroid Activity of 5 Iodo 2 Thiouracil. Thi drug (ITU) reputedly is without goitrogenicity R C Goldberg and J Wolff (Harvard Univ) found normal alpha cells in pituitary glands of rats treated with 0 2% ITU This was interpreted to mean that thyroid hormone synthesis was not completely blocked Administration of 0 16% ITU re sulted in a growth rate less than that of control rats but greater than that of rats in which thyroid hormone synthesis was totally suppres ed

Administration of 1% ITU for one month resulted in thy roid glands that were hypertrophied to the same extent as those of rats receiving 0 1% propylthiouracil The microscopic picture was also similar The pituitary glands showed com plete alpha cell degranulation The growth curve was identical to that obtained with thiouracil (TU)

The release rate of organic I^{131} a reliable index of rate of thyroid activity was affected to the same extent by 1% ITU as by 0 1% TU The thyroid (total) iodine content of rats treated with 1% ITU was significantly increased but organic

(5) E doc logy 54 181 19 F b ry 19 4

mission of hyperthyroidism has been induced by treatment with an antithyroid drug

The long follow up period has shown that only 49% of recrudescences occur within 2 months 60% within 6 months and 80% within 18 months

Late Results of Treatment of Thyrotoxicosis with Thiouracil Compounds Doris I Manson[4] (Univ of Aberdeen) treated 112 patients with thiouracil methylthiouracil and propylthiouracil The initial dose was 400 600 mg 200-400 mg and 100 400 mg respectively Maintenance dose was 100 mg

THYROIDECTOMY IN 30 CASES

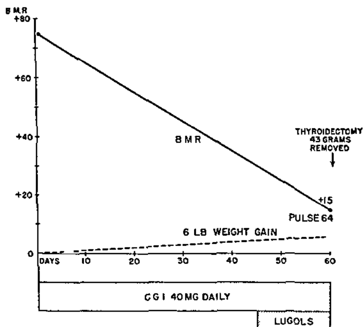
REASONS	PATIENTS
Nodular goiter	10
Older age groups	2
Tracheal compression	4
Large goiter	1
Severe degree of thyrotoxicosis	4
Patients preference	2
Toxic reactions to thiouracil	2
Poor response to thiouracil	4
Difficult to stabilize	1

50 25 mg and 25 mg respectively Progress was determined by frequent clinical examination Subtotal thyroidectomy following short term medical treatment was performed on 30 patients for reasons shown in the table Nine are still being treated and one concluded a course of propylthiouracil One patient died of agranulocytosis and another committed suicide

Of the remaining 70 43 (61%) had no recurrence for more than a year after discontinuance of the drug Relapse after varying periods occurred in 27 patients 11 of whom were prepared for operation 15 had a further trial of long term thiouracil therapy and 1 died in thyroid crisis Of the 15 who began a second course of thiouracil 1 developed severe granulopenia 2 responded poorly and were operated on Of the remaining 12 5 had no relapse 2 had a third course of thiouracil and 5 were prepared for operation

The remission rate after the first course of thiouracil was 61% after a second course only 42% Those who had a relapse after one adequate course are likely to have a relapse after a second course The relapse rate is higher in the under

(4) Ed b gh M J 60 321 330 J ly 1953



F g 98 —Cl l ponse t neom ca l f w ma 64 w th primary h p thy d sm fo yea d w ght l f 40 lb Aft 60 d y f t tment BMR w rmal d p f 1[or] d ly (Courtesy f B tel E C J Cl E doc l 13 1305 1311 N mbe 1953)

Reactions to Neomercazole in Primary Hyperthyroidism

P	Ag Sex	D Do (Mg)	D O R ct n	T React on
1	59 F	40	42	Moderate nonprurit c ery thematous rash
2	3? F	50	14	Severe urticarial rash angioneurot c edema and arthralgia
3	3? F	40	24	Agranulocytosis

(table) the incidence is similar to that observed with tapazole® (6%) Of the two skin reactions that occurred one was very severe and the other was not sufficiently severe to necessitate complete withdrawal of the drug In the third case recovery from agranulocytosis followed withdrawal of the drug and administration of antibiotics

iodine content was reduced to the same level as that in rats treated with 0.1% TU. There was no evidence that ITU inhibits either the release of thyroid stimulating hormone or its action in stimulating the thyroid.

In rats placed on a diet containing 0.025% TU the goitrogenic activity was almost completely reversed by the addition of iodide. Weak antithyroid activity without marked goitrogenicity may result from the combined action of the breakdown products of ITU (TU and I).

[The effects of iodothiouracil are explained entirely by the sum of the effects of thiouracil and iodine released by decomposition of the drug. Since the toxicity of thiouracil is higher than that of propylthiouracil or methimazole, the clinical use of iodothiouracil seems unjustified.—Ed.]

Clinical Experience with New Antithyroid Drug 2-Carbethoxythio-1-Methylglyoxaline. Elmer C. Bartels[6] (Lahey Clinic) administered this drug, neomercazole (Fig. 97), to 40

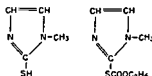


Fig. 97.—C mpa s of tructu al formula of tapa l * (m th mazol) w th th t of n om ca le In th l tte , the hyd og n atom th tap le struct e replaced by a carb th y g oup (Court sy of Bartels E C J Cl n E docrn l 13 1305 1311 Nov mb r 1953.)

patients with primary hyperthyroidism and 12 with adenomatous goiter with hyperthyroidism. All but three patients were females and ages ranged from childhood to the seventh decade. Maximal weight loss was 60 lb. The BMR of 22 patients was + 40% or over (up to + 74%). It was found that in a patient with primary hyperthyroidism and a small goiter 30 mg. daily was needed to produce a response equivalent to 300 mg. propylthiouracil or 30 mg. tapazole.* With a large goiter 40 mg. daily was needed (Fig. 98). Patients with adenomatous goiters required 40-50 mg. neomercazole daily to obtain the antithyroid effect desired.

Untoward reactions were observed in three patients

(6) J Cl E d n ol 13 1305 1311 N mber 1953

Effect of Radioactive Iodine Alone and in Combination with Methylthiouracil on Tumor Production in the Rat's Thyroid Gland Using 100 rats I Doniach[8] (Postgrad Med School London) tested the carcinogenic effect on the thyroid gland of 5 30 and 100 μc I^{131} alone and combined with methylthiouracil subsequently for a 15 month course The I^{131} increased the formation of thyroid adenomas by comparison with controls in the 5 and 30 μc groups but not in the 100 μc group Of 20 rats treated with 30 μc I^{131} and methylthiouracil combined 5 had thyroid carcinoma The dosage range to the thyroid—2 270 16 200 rep—is likely to include the dosage aimed at—about 9 000 rep—in the treatment of Graves disease The carcinogenic danger of I^{131} therapy is attributed to irreversible thyroid cell changes which make such cells more susceptible than normal cells to tumor formation when stimulated to undergo hyperplasia

An I^{131} dose that would suffice to cure Graves disease might interfere enough with thyroxin synthesis to lead to increased output of thyrotropic hormone which when combined with the initial radiation damage might lead to tumor production The use of antithyroid drugs in a relapse after radiation therapy might further stimulate tumor formation Among precautions to be observed in treating Graves disease are (1) that I^{131} be used in thyrotoxic patients under 45 only when other methods are contraindicated or when life expectancy is less than 20 years (2) that the minimal dose of I^{131} to produce remission be administered (3) that thyroxin medication be instituted and maintained after relief of thyrotoxic symptoms and (4) that antithyroid drugs strongly contraindicated at any time after radioiodine therapy be avoided

The carcinogenic danger to man of I^{131} therapy in Graves disease is by no means proved by the experiments in the rat (1) since comparable susceptibility to thyroid neoplasia in the two species is not known (2) since direct comparison of radiation dosages is not possible and (3) since it cannot be assumed that the methylthiouracil stimulated thyroid gland of the rat is similar to the thyrotoxic gland of man Nevertheless the observations warrant serious consideration the I^{131} dosage

(8) B r J C 7 181 0 J 1953

Despite its strong antithyroid qualities neomercazole is not the ideal drug

[This new drug has produced agranulocytosis (Harrison Lancet 1 396 Feb 20 1954) and fatal bone marrow aplasia (Richardson et al Brit M J 1 364 Feb 13 1954) It is probably a good deal more dangerous than methimazole or propylthiouracil —Ed]

Loss of Taste as Toxic Effect of Methimazole (Tapazole®) Therapy Report of Three Cases Clinical studies have shown methimazole to be the most potent antithyroid compound now available Fewer toxic reactions than accompany administration of other agents might be expected because its high potency suggests that smaller doses would be required Early reports indicated that incidence of toxicity from methimazole is about the same as that from propylthiouracil

Bernard L Hallman and J Willis Hurst[7] (Emory Univ) observed three patients who had complete loss of taste during therapy with methimazole One patient also lost the sense of smell Senses gradually returned to normal two or three weeks after the drug was stopped The site of the lesion could not be localized

Loss of taste has also been reported as an effect of methylthiouracil Hysteria is probably the commonest explanation for the development of ageusia but in these patients the authors considered it an unlikely cause Peripheral nerve damage can produce ageusia by (1) bilateral involvement of the gustatory function of the 7th 9th and 10th cranial nerves and (2) by means of a unilateral facial nerve lesion which obtunds taste sensation on one side of the tongue with complete subjective ageusia resulting from hysteria It is also possible to have complete loss of taste from an oblongatal lesion of the nuclear region of the 9th nerve In this situation the roots are usually bilaterally affected it may sometimes be seen in multiple sclerosis and syringomyelia Since no other neurologic lesions were present involvement of the sensory receptors themselves would seem to be the most logical explanation of the sensory defects of the three patients reported on There was no evidence of damage or inflammation on physical examination

[Similar loss of taste was reported after methylthiouracil therapy by Schneeberg (J A M A 149 1091 July 19 1952) —Ed]

(7) J A M A 152 322 May 23 1953

be due to inability of the thyroid to complete the synthesis of the hormone This defect has apparently not been previously described

Most of the observations of I^{131} and some of the quantities of protein bound iodine found in the plasma suggested hyper thyroidism and might readily have been attributed to thyro toxicosis had the clinical picture been ignored whereas the amounts excreted in the urine were consistent with hypo thyroidism It is important that no laboratory test result take precedence over the clinical assessment of the patient

[Similar studies have also been published by Wilkins Clayton and Berthrong (Pediatrics 13 235 1954) —Ed]

Use of Thyrotropin in Differential Diagnosis of Primary and Secondary Hypothyroidism. Bengt Skanse[1] (Univ of Lund) studied the functional state of the thyroid before and after administration of thyrotropic hormone (TSH) in 10 *euthyroid patients 10 patients with primary myxedema and 8* with hypopituitarism Procedures carried out in each patient *before and after stimulation with TSH were determinations* of serum protein bound iodine (PBI) basal metabolic rate (BMR) and serum cholesterol level measurement of urinary excretion of I^{131} and determination of extrarenal disposal rate of I^{131} (ERDR) obtained from analyses of the curves of uri nary excretion of I^{131} according to Keating *et al* Thyrotropin (actyron) was administered intramuscularly 20 units daily for six or more days

In euthyroid patients administration of TSH for six days caused a considerable decrease in the 48 hour urinary excre tion of I^{131} All individual values fell within the range sug gestive of thyroid hyperfunction The ERDR increased from an average of 4 6% to 19 6%/hour All individual values were within the range observed by Keating *et al* in hyperthyroid patients In seven cases the PBI values rose considerably after TSH administration The BMR was increased in four Clinically there were no signs or symptoms of thyrotoxicosis

In patients with primary thyroid myxedema administra tion of TSH for at least six days caused no change in the 48 hour urinary excretion of I^{131} The average was 78 5% as compared with 77 4% before TSH administration There was no change in ERDR

(1) A t d l 13 358 370 1953

now used in treating Graves disease may eventually prove carcinogenic

[Although these animal experiments may not apply to human beings, the fact that the intensity of radiation used therapeutically in humans is carcinogenic in rats is disturbing Follow up studies of radioiodine-treated patients will have to be continued for many years before one will feel safe in prescribing this type of treatment for patients with a prolonged life expectancy —Ed]

↓ The clinical use of I^{131} has begun to clarify our understanding of the mechanisms of defective hormone production The following five papers present studies of the hypothyroid state by this technic.—Ed.

Radioactive Iodine Studies in Nonendemic Goitrous Cretinism E M McGirr and James H Hutchison[9] (Glasgow) report their experience with 12 patients aged 3 20 Four were members of one family and three were closely related to them Two were members of another family and three were unrelated to either family or to each other The patients were typically hypothyroid although none of them came from an area of endemic goiter and none had a history of iodine deprivation or exposure to a goitrogen

Carrier free I^{131} 30 200 μc was given in water as a drink to each patient two hours after food The glands did not retain the radioiodine but released it into the circulation In six cases measurements showed that the glands accumulated iodine more rapidly than normal Six of eight patients excreted in the urine more than 25% of the ingested dose in 6-24 hours a finding which some workers consider characteristic of hypothyroidism In eight of nine patients total radioactivity present in the plasma at 48 hours exceeded 0 7%/L protein bound iodine at 48 hours obtained by trichloroacetic acid precipitation yielded 0 1 0 5%/L in five and more than 0 5% in four Goodwin *et al* consider a value of over 0 5% at 48 hours as indicating thyrotoxicosis

Chromatographic studies in one case supported the opinion that the thyroid hormone whether thyroxin or triiodothyronine was not being released into the circulation It is reasonable to assume that radioactivity was present in a small protein molecule Plasma studies confirmed the conclusion that the thyroid could take up inorganic iodine from the blood and convert it into an organic compound No glands were examined histologically since no thyroidectomies were necessary It appears that nonendemic goitrous cretinism may

(9) Lancet 1 1117 1120 J n 6 1953

Hypothyroidism Due to Thyrotrophin Deficiency without Other Manifestations of Hypopituitarism Charles R Shuman[2] (Temple Univ) reports a case

Woman 64 was hospitalized in 1946 with a diagnosis of diabetes mellitus diabetic neuropathy and depressive psychosis Clinically she appeared to have myxedema but the BMR was —8% The cholesterol level was 410 mg /100 cc The diabetes was brought under control with diet and 38 units protamine zinc insulin daily She was hospitalized again in January 1952 with severe polyuria and thirst There was diabetic and hypertensive retinopathy with many scattered punctate hemorrhages absorbing exudates and sclerosis of the arterioles The blood pressure was 190/110 No thyroid tissue could be palpated in the neck Diabetic stabilization was achieved with 230 units insulin daily and a diet containing 70 Gm protein 60 Gm fat and 150 Gm carbohydrate

After a course of shock therapy for depression the insulin requirement fell to 120 units/day The thyroid gland accumulated negligible amounts of iodine in 24 hours after an 80 μc dose of I^{131} She was discharged with instructions for medication which she did not follow In March 1952 she was re admitted because of diabetic acidosis Diabetic control was re established and she was stabilized on 140 units of NPH insulin daily Normal 17 ketosteroid values and normal eosinophil responses to epinephrine and ACTH indicated that the adrenal cortex and the portion of the anterior pituitary concerned with ACTH elaboration were not affected Desiccated thyroid therapy was instituted (60 mg four times daily) The pulse rate was 72 86 blood pressure 150/80 and NPH do age was gradually reduced to 40 units/day The urine remained virtually sugar free and the blood sugar level was 194 mg /100 cc Administration of thyroid stimulating hormone resulted in a marked increase in I^{131} uptake by the thyroid gland and a high thyroidal iodine clearance and conversion ratio

The myxedema in this patient must have been the result of an isolated thyrotrophin deficiency Others have shown that thyrotrophin adrenocorticotrophin and gonadotrophic hormones are produced by distinct cells in the anterior pituitary of the rat The existence of cells devoted solely to the elaboration of specific hormones permits the suggestion of an isolated defect in this case

High PBI[131] Concentration in Blood of Patients with Myxedema Preliminary Report P S Blom and J Terpstra[3] (University Hosp Leiden) discuss two cases of hypothyroidism following thyroidectomy In one patient the pulse rate was 56 the BMR — 20% serum cholesterol level 312 mg /100

(2) J Cl E loc l 13 795 800 J ly 1953
(3) Ibid pp 989 993 A g st 1953

All patients with pituitary myxedema presented definite clinical and laboratory evidence of pituitary disease Diagnosis was verified in three cases by operation In one case the studies were done after hypophysectomy performed in an attempt to treat widespread metastases from a carcinoma of the breast

CASE 21 —Man 60 was hospitalized because of a tuberculous lymphadenitis in the left supraclavicular fossa Puberty started at age 18 and at age 22 he began to shave once a week The physical appearance was that of hypopituitarism X ray examination of the sella turcica showed enlargement with displacement of the clinoids Urinary excretion of 17 ketosteroids was 3 2 mg /24 hours Excretions of 11 oxysteroids was 0 60 mg /24 hours Urinary gonadotrophins were less than 10 m u /24 hours An insulin tolerance test showed no hypoglycemic response Diagnosis was hypopituitarism probably due to chromophobe adenoma

CASE 22 —Boy 17 had begun to show retardation of growth at age 3 He had no axillary or pubic hair Urinary excretion of 17 ketosteroids was 1 3 mg /24 hours and excretion of 11 oxysteroids 0 24/24 hours Urinary gonadotrophins were less than 10 m u /24 hours Pituitary dwarfism was diagnosed

CASE 24 —Woman 58 showed a definite enlargement of the sella turcica on x ray study at age 22 There was loss of axillary and pubic hair Temporal hemianopsia was present on the right side Urinary 17 ketosteroid excretion was 3 mg /24 hours and 11 oxysteroid excretion 0 37 mg /24 hours Urinary gonadotrophins were very low Diagnosis was pituitary tumor with hypopituitarism

Following TSH administration for at least six days to the patients with pituitary myxedema the 48 hour urinary excretion of I^{131} decreased to 30 6% (range 15 45 3%) The ERDR increased to 13%/hour (range 5 1 31 1%) In every patient there was a definite increase in ERDR In six patients the rate increased to values of the order observed by Keating *et al* in patients with adenomatous goiter and hyperthyroidism and in two the values were in the range of euthyroidism

There is a case on record of a patient with hypopituitarism of long standing in whom no response to TSH was elicited Perloff *et al* reported a thyroid response in a patient with hypopituitarism of 28 years duration and in the present study a response was obtained in patients with pituitary disease of 10 15 and 35 years' duration This would suggest that lack of response by thyroid due to long standing hypopituitarism is unusual

nodular in three cases the pyramidal lobes were palpable and in three the Delphian lymph nodes were enlarged Total serum protein bound iodine (PBI) concentration was ab normally high in three cases and in two of these the butanol extractable thyroxin like iodine (BEI) was normal Surgical exploration with subtotal thyroidectomy was performed in four cases with histologic study and biopsy specimens ob tained with the Silverman needle were examined in the other two Typical lymphocytic thyroiditis was found in all

Early in the study of children with nontoxic goiters surg ical exploration was done to rule out carcinoma As the clin ical characteristics of chronic lymphocytic thyroiditis in chil dren were more fully recognized needle biopsy was substi tuted if a diagnosis of this condition seemed likely Later the tendency was to omit biopsy if the goiter could be made to disappear with generous maintenance doses of thyroid

Thyroid USP (100 200 mg /sq m body surface/day) was administered to three patients and in two there was consid erable shrinkage of the goiter total PBI values fell and BEI values rose to midnormal levels In the third case the total PBI value fell but there was no shrinkage of the goiter and BEI was at a low normal adult level

The condition may be characterized by disorders of thy roid hormone release as demonstrated by abnormal relations between total serum PBI and BEI values and a tendency to hypothyroidism The fact that generous maintenance doses of thyroid can cause the goiter to subside suggests that it is compensatory The authors postulate that in thyroiditis the follicles release either partially proteolyzed or unproteolyzed thyroglobulin or noncalorigenic compounds similar to diiodo tyrosine or both into the circulation There is then a tendency to thyroid hormone lack increased pituitary thyroid stimulat ing hormone production enlargement of the gland and in creased secretion of thyroidal substances into the circulation This continues irrespective of goiter formation or of total serum PBI level until the concentration of metabolically active thyroid hormone (BEI) reaches physiologically satisfactory levels Such a sequence of events accounts for the simultaneous occurrence of clinical euthyroidism goiter elevated PBI and normal BEI values The fact that thyroid therapy can elimi

ml and the concentration of protein bound iodine (PBI) 1.3 μg/100 ml The other patient had a pulse rate of 60 BMR of −16% serum cholesterol level 475 mg and PBI 1.3 μg In both cases the total radioactivity in the serum and the protein bound fraction (% dose/L) after the administration of I^{131} was abnormally high

To account for this phenomenon the assumption is made that after thyroidectomy only very small remnants of thyroid gland tissue are left functioning and that these remnants (under continuing and perhaps increasing stimulation by thyroid stimulating hormone) preserve the typical properties of the total gland in hyperthyroidism An essential feature of these glands is the rapid turnover rate of iodine with only slight storage of organically bound iodine The total iodine content in a hyperfunctioning gland is considerably less than in a normal gland (In the very small remnants in these cases this glandular pool must have been extremely small) As a consequence all radioiodide collected by these remnants will be quickly transferred to the blood after being transformed into radiothyroxin

Since the functioning remnant of thyroid is small however the total amount of thyroid hormone formed is insufficient to maintain normal concentrations of PBI As a result a low PBI and hypothyroidism are combined with a high concentration of I^{131} in the small amount of PBI which is actually secreted

[The rapid appearance of serum protein bound I^{131} in the circumstances described by the authors would be easy to interpret if simultaneous thyroid or urine counts were made However where complete reliance is placed on the blood counts alone (e g Macgregor *et al* p 576) confusion might result —Ed]

Goiter Due to Lymphocytic Thyroiditis (Hashimoto's Struma) Its Occurrence in Preadolescent and Adolescent Girls Donald Gribetz Nathan B Talbot and John D Crawford[4] (Harvard Med School) report six cases of this condition in girls aged 9 13 The disease was formerly considered rare in patients under 20 Only one patient had mild dysphagia and in only one was skeletal maturation retarded a change suggesting hypothyroidism The thyroid glands were two to four times larger than normal and were firm easily outlined and of coarsely granular consistency Three of the goiters were

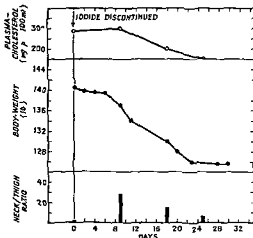
(4) New England J Med 250 555 557 Ap 1 1954

acetate saline and cortisone in another) could revive the pa tients

[One might speculate as to whether this coma is a manifestation of hypopituitarism This seems unlikely since cortisone was ineffective Severe hypothermia leading to coma and death has been described in rats by LeBlond and Early (Endocrinology 51 26 July 195?) but it occurs only when extreme degrees of thyroid deficiency have been produced The patients failure to respond to thyroxin might reflect inability to de iodinate this hormone to triiodothyronine rapidly enough to restore normal function It would be interesting to study the effects of the latter hormone in this syndrome in which speed of action is of the utmost importance—Ed]

Two Cases of Myxedema Attributed to Iodide Administration are reported by M E Morgans and W R Trotter[6] (London)

Woman 45 was hospitalized because of a 14 lb gain in weight



Fg 99—Pl ma ch l t l l l body w ght d d d uptak ft m f d d f m mp d tak f r thm (Co t y f M rg M E d T tt W R L n t 2 1335 1337 D c 6 1953)

in three or four months swelling of the abdomen face and hands fatigue and greater sensitivity to cold She was asthmatic and had been taking a mixture containing 7½ gr sodium iodide at least every four hours and sometimes oftener over the previou four years Examination revealed a pale l thargic woman with puffiness around the eyes and edema of both legs which pit with difficulty The skin

(6) L t 133 1337 D 26 1953

nate the goiter and lower total PBI while raising BEI values lends further support to this thesis

[Is this lymphoid infiltration truly a Hashimoto struma or does it merely represent an inflammatory reaction to prolonged overstimulation of a gland producing defective and physiologically ineffective hormone? The analogy between this circumstance and that seen in the adrenogenital syndrome (see pp 612 f) is most instructive—Ed]

Myxedema Coma Coma as a terminal event in the natural history of myxedema is hardly mentioned in modern texts V K Summers[5] (Liverpool) reports on four patients with myxedema and terminal coma Diagnosis was confirmed at autopsy

CASE 1—Man 59 a few days after hospital admission had a rectal temperature of 83 F Thyroid orally and thyroxin sodium subcutaneously were ineffective and death occurred shortly after

CASE 2—Woman 65 had a vaginal temperature of 75 F within 48 hours after admission Thyroxin sodium 2 mg every six hours subcutaneously had no effect Immersion in a hot bath raised the vaginal temperature to 98 6 F but the patient died the following day

CASE 3—Man 63 became drowsy within 48 hours of admission. Desiccated thyroid 1 gr three times daily by mouth and cortisone 100 mg and desoxycorticosterone acetate 10 mg intravenously by saline drip were without effect He was stuporous on the following day and the rectal temperature was only 87 5 F Thyroxin sodium 2 mg every six hours was substituted for thyroid cortisone was continued and the patient was immersed in a hot bath Temperature rose to 98 6 F He became worse and a further 200 mg cortisone was given but death occurred the next day

CASE 4—Man 59 had a rectal temperature of 83 5 F on admission Treatment with thyroxin odium 1 mg and cortisone 100 mg every six hours was ineffective and he died in 48 hours

Diagnosis of myxedema coma is easy but differentiation from hypopituitary coma especially when myxedema features are prominent may be difficult In the common postpartum type of hypopituitarism the history will clarify the diagnosis

Although it could be suggested that hypothermia is the cause of coma in these cases and that the low temperatures are due to depression of metabolism by loss of thyroid secretion in only one case in which development of coma was presumed likely was it possible to restore the patient with thyroid extract or thyroxin sodium Once coma had developed neither thyroxin alone nor in combination with hydrotherapy or any other drug (cortisone in one case and desoxycorticosterone

(5) B M J 2 366 368 Aug 15 1953

widely differing estimates of the incidence of thyroid malignancy The surgical clinics In the next two papers Sokal attacks this problem —Ed]

Evolution of Nodular Goiter Simple goiter occurs sporadically and endemically all over the world Simple goiter almost always progresses to the nodular form which in turn may become the seat of hyperthyroidism The possible relation between thyroid cancer and nodular goiter makes a study of the latter mandatory according to Selwyn Taylor[8] (Postgrad Med School London)

Patients with nontoxic goiters (no hyperthyroidism or malignancy) who were to undergo thyroidectomy were given a tracer dose of radioactive iodine and after operation radioautographs were prepared from sections made through whole lobes Comparison of the histologic patterns and iodine uptake showed correlation between the blackening of the radioautograph and characteristics in the follicles

The earliest stage of simple goiter seen in young patients from an endemic area was represented by diffuse hyperplasia with uniformly increased iodine uptake throughout the gland This occurs when the iodine content of the diet is low and is probably associated with some goitrogenic substance in the diet The goiter can be prevented by administration of additional iodine and the thyroid enlargement reversed but not if the gland has been enlarged for a year

In older patients iodine uptake was confined to discrete areas of great activity as shown by intense blackening on the radioautograph Histologically the areas were composed of groups of follicles of uniformly small diameter with tall cells and prominent nuclei Rarely there was only a single area of hyperactivity

All areas of hyperactivity progressed to a stage of central hemorrhage and necrosis losing their capacity to take up iodine Fresh areas of activity then appeared Multinodular goiters represent the continued repetition of this process Multiple nodules can be palpated in almost all goiters by the time the patient reaches 40 The proportion of inactive to active areas increases with age Histologically burned out nodules vary in appearance (a group of follicles with flattened cells a large solitary colloid filled follicle a cyst or evidence of old hemorrhage fibrosis or calcification)

(8) J Cl E doc 1 13 123 1247 Octob 1953

was rough Occasional rhonchi were noted The thyroid gland was diffusely enlarged and extremely firm on palpation it was not abnormally vascular and moved easily on swallowing Clinical diagnosis was myxedema possibly associated with Hashimoto thyroiditis BMR was —21% the plasma cholesterol level was 300 mg /100 ml Chest radiography showed a heart shape compatible with myxedema The iodine was omitted from the patient s medicine and during the ensuing three to four weeks a dramatic change occurred Edema and puffiness disappeared and body weight fell from 140 to 126 lb with diuresis maximal on the sixth day after iodide withdrawal Plasma cholesterol level fell to 150 mg /100 ml (Fig 99) A chest x ray showed a reduction in heart size Radioiodine measurements indicated a *practically zero uptake 24 hours after* withdrawal of the iodide Nine days later the values were in the thyrotoxic range with a return to normal 25 days after iodide was discontinued

The iodide apparently had an antithyroid action causing blockage of thyroxin formation and consequent hyperplasia of the gland and myxedema

[It is usually felt that iodides cannot produce hypothyroidism When extremely large doses are taken however ordinary criteria do not apply —Ed.]

Goiter and Hypothyroidism Developing during Treatment with PAS H T Davies and H J B Galbraith[7] (St Bartholomew s Hosp) note that para aminosalicylic acid (PAS) has a definite though feeble antithyroid action similar to that of thiouracil drugs and in a few patients receiving it goiter and possibly hypothyroidism may develop without dosage being excessive or treatment prolonged The process is reversible if PAS is stopped before myxedema is severe

Man 28 with pulmonary tuberculosis was given 56 Gm streptomycin and 1 600 Gm PAS over five months when a symptomless diffuse nontender goiter was noted Serum cholesterol value was *220 mg /100 cc* and BMR —10% Streptomycin and PAS were discontinued and isoniazid was begun A few days later BMR was —21% and serum cholesterol level 268 mg /100 cc Radioactive iodine studies revealed excessive thyroid activity with no corresponding increase in rate of organic binding of iodine Four weeks after discontinuation of PAS the goiter was just palpable and BMR was — 1% Four months later the thyroid was still just palpable BMR was + 5% and serum cholesterol level 215 mg /100 cc

[The possibility of this complication was discussed by Hanngren (1953 54 YEAR BOOK p 609) It will doubtless continue to be a problem for phthisiologists —Ed]

↓ It is generally agreed that thyroid cancers should be excised but there is violent controversy as to the proper treatment of thyroid *nodules* which are not obviously malignant Most of this disagreement hinges on

(7) Brit M. J 1 1261 Jun 6 1953

months In two patients the goiter returned after treatment was discontinued Only 6 of the 40 patients not treated with desiccated thyroid showed a decrease in the size of the gland

Thyroid exerts a beneficial effect on the size of the goiter in three out of four cases and aids in diagnosis since failure of the goiter to respond and failure of radioiodine accumulation to be suppressed constitutes suggestive evidence for a diagnosis of hyperthyroidism The response of a single nodule to thyroid indicates that its hyperplastic state is physiologic and not neoplastic

ACTH and Cortisone Therapy of Acute Nonsuppurative (Subacute) Thyroiditis Sidney C Werner[1] (Columbia Univ) studied two men and four women with clinical and laboratory evidence (high sedimentation rate greatly reduced thyroidal uptake of I^{131} in 24 hours) of thyroiditis ACTH or cortisone in varying doses was given every six hours Subsidence of temperature loss of tenderness of the gland decrease in size and restoration of a sense of well being followed within 10-24 hours after use of ACTH and within 48 72 hours after cortisone

Woman 44 was hospitalized with a temperature of 102 F She had a small thyroid with definite tenderness on the right White blood cells numbered 18 160 sedimentation rate was 74 108 mm /hour BMR + 18% thyroidal I^{131} uptake at 24 hours 13% (on entry with right lobe involvement only) then 3% 16 days later (upon involvement of the left lobe) Cortisone 25 mg intramuscularly every six hours for four days was given The temperature fell after 48 hours and the thyroid became small and nontender There was a recurrence five days later with apparent left lobe involvement in addition ACTH 10 mg was given intramuscularly every six hours on the first day followed by 20 mg every six hours for the next three days The same dramatic relief as with cortisone ensued within 12 hours Symptoms and signs recurred 10 days after treatment was stopped Under x ray therapy she recovered two weeks later

ACTH or cortisone therapy in acute nonsuppurative thyroiditis results in dramatic relief of the systemic and local signs Therapy does not appear to interfere with the spontaneous recovery which characterizes the disorder The difficulty in assessing the cortisone effect is illustrated in Figure 100 which shows the spontaneous rise and fall of temperature from the 12th to the 18th day of illness without any treatment

(1) J Cl E d 1 13 133 1340 N mbe 1953

Treatment of Simple Goiter with Thyroid The first published results of thyroid administration in this disease were by Reinhold in 1894 About the same time and independently P Bruns professor of surgery at Tubingen published his first report on 12 goitrous patients

Monte A Greer and E B Astwood[9] (Boston) report on 50 patients seen over five years and followed for a sufficiently long interval Diagnosis in each case was simple nontoxic goiter The usual thyroid dose was 2 or 3 gr daily with extremes of ½ and 6 gr daily Radioactive iodine uptake was determined on more than half the patients Dosage was increased if the 24 hour uptake was not suppressed below 10% of the quantity given It was possible to re examine 40 patients with simple nontoxic goiter who received no therapy

Of the patients treated 24% failed to show any response and all the others had a regression in thyroid size which was complete in 40% Multinodular goiters and single nodules responded less favorably than diffuse goiters However in 27 patients with multinodular goiters or single nodules only one third failed to show some effect Among the 40 who received no thyroid therapy only 6 had a decrease in thyroid size

The size of the goiter did not influence response to therapy except that patients with great thyroid enlargement were less likely to experience complete regression None of the patients with nodular goiter and great enlargement and only one with diffuse goiter had a complete remission Age was not a factor in response to treatment Of the 18 patients with diffuse goiter studied with radioiodine 6 had a 24 hour accumulation in the thyroid gland of more than 50% of the dose Response to thyroid therapy did not seem to depend on the length of time the goiter had been present contrary to reports by others Of the diffuse and multinodular goiters that disappeared completely one third had been present for less than 1 year and one third for more than 10 years Of the single nodules that underwent remission all but one had been present less than one year There was no difference among the three types of goiters with regard to length of time required for them to disappear completely with therapy Most complete remissions occurred within three to six

(9) J Cl n E d c 1 13 1312 1331 No mb 1953

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Thyroid exerts a beneficial effect on the size of the goiter in three out of four cases and aids in diagnosis since failure of the goiter to respond and failure of radioiodine accumulation to be suppressed constitutes suggestive evidence for a diagnosis of hyperthyroidism The response of a single nodule to thyroid indicates that its hyperplastic state is physiologic and not neoplastic

ACTH and Cortisone Therapy of Acute Nonsuppurative (Subacute) Thyroiditis Sidney C Werner[1] (Columbia Univ) studied two men and four women with clinical and laboratory evidence (high sedimentation rate greatly reduced thyroidal uptake of I^{131} in 24 hours) of thyroiditis ACTH or cortisone in varying doses was given every six hours Subsidence of temperature loss of tenderness of the gland decrease in size and restoration of a sense of well being followed within 10-24 hours after use of ACTH and within 48 72 hours after cortisone

Woman 44 was hospitalized with a temperature of 102 F She had a small thyroid with definite tenderness on the right White blood cells numbered 18 160 sedimentation rate was 74 108 mm /hour BMR + 18% thyroidal I^{131} uptake at 24 hours 13% (on entry with right lobe involvement only) then 3% 16 days later (upon involvement of the left lobe) Cortisone 25 mg intramuscularly every six hours for four days wa given The temperature fell after 48 hours and the thyroid became small and nontender There was a recurrence five days later with apparent left lobe involvement in addition ACTH 10 mg was given intramuscularly every six *hours on the first day* followed by *20 mg* every six hours for the next three days The same dramatic relief as with cortisone ensued within 12 hours Symptoms and signs recurred 10 days after treatment was stopped Under x ray therapy she recovered two weeks later

ACTH or cortisone therapy in acute nonsuppurative thyroiditis results in dramatic relief of the systemic and local signs Therapy does not appear to interfere with the spontaneous recovery which characterizes the disorder The difficulty in assessing the cortisone effect is illustrated in Figure 100 which shows the spontaneous rise and fall of temperature from the 12th to the 18th day of illness without any treatment

(1) J Cl E docr 1 13 133 1340 N mbe 1953

ACTH or cortisone dosage should be kept as low as is consistent with a therapeutic effect to avoid complications Efforts to reduce the dosage should be made periodically and treatment should be stopped on signs of remission The disease may last 12 weeks or more before spontaneous remission

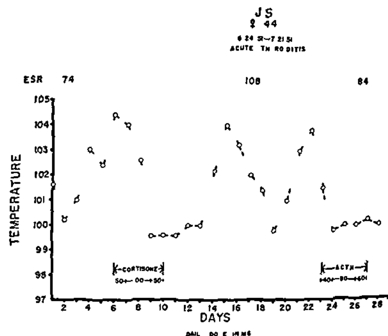


Fig 100—(Co t sy of Werne S C J Cl E docr ol 13 133 1340 November 1953)

occurs All treated patients should be followed with care particularly with reference to possible prolongation of the course of illness following use of ACTH or cortisone and increased incidence of chronic thyroiditis however there was no evidence of these complications in the present series

Present Day Problem of Cancer of Thyroid is discussed by Richard B Cattell and Bentley P Colcock [2] who reviewed the records of 78 histologically proved cases of cancer of the thyroid a 5 3% incidence among all thyroid operations at

(?) J Cl n Endoc nol 13 1408 1415 No mbe 1953

Lahey Clinic in 1951 52 Of 1 479 patients with thyroid diseases 447 had primary hyperthyroidism and no evidence of cancer and 93 had thyroiditis without cancer A discrete single adenoma of fetal or follicular type was found in 104 patients whereas 644 had diffuse nontoxic nodular goiter Diffuse nodular goiter with secondary hyperthyroidism was found in 113 patients Of the 748 patients with nontoxic nodular goiter 76 (10 2%) had cancer Of 113 patients with toxic nodular goiter 2 (1 8%) had cancer Over all incidence of thyroid carcinoma in relation to nodular goiter was 0 1% More than half of the 78 cancer patients were under 45 and the ratio of men to women was 3 8 There was equal incidence of right and left lobe involvement

Since there are no diagnostic signs of cancer a high index of suspicion must be maintained for any nodular involvement of the gland In 11 patients the thyroid carcinoma was apparent clinically All of the 52 patients with preoperative diagnosis of discrete or solitary adenoma were proved to have carcinoma Incidence of carcinoma among the 156 patients with solitary nodules was 33 3%

Comparison of the data in this series with those in the literature suggests that the incidence of thyroid carcinoma is increasing Because clinical diagnosis is so difficult it is essential to advise the removal of all discrete thyroid nodules Frozen section is imperative whenever there is any suspicion of carcinoma

Pre existing goiter was found in 58 of the 78 patients with carcinoma in 9 it was discovered on routine examination There were 4 patients with malignant adenoma 37 with papillary elements predominating and 19 with alveolar carcinoma including follicular or adenocarcinoma and Hurthle cell tumors There were small cell and giant cell tumors in 18 patients with carcinoma simplex

Excision or subtotal hemithyroidectomy was carried out in 12 patients lobectomy in 9 total thyroidectomy in 3 and biopsy alone in 7 Neck dissection was considered necessary in approximately half of all patients with thyroid carcinoma High voltage x ray therapy was recommended in all advanced cases and 55 of the 78 patients were so treated There was no operative mortality but 9 of the 78 patients died of carcinoma

Carcinoma of Thyroid Gland James D Majarakis Danely P Slaughter and Warren H Cole[3] report that during 1936 52 75 carcinomatous goiters were found at 1 429 thyroidectomies (an incidence of 5 2%) at Illinois Research Hospital The incidence of carcinoma in 580 cases of toxic diffuse goiter was 0 1% in 401 of toxic nodular goiter 1% and in 448 of non toxic nodular goiter 15 6% (20 9% in solitary nontoxic and 8 7% in multinodular nontoxic nodular goiter) Despite an increase in the number of operations for nontoxic nodular goiter during 1945 52 the number of thyroid carcinomas operated on did not increase—4 2/year during 1936-44 and 4 6/year during 1945 52 The increase in operations for non toxic nodular goiters was due in part to a change in policy in 1945 that all patients with such goiters have a thyroidectomy because of the high incidence of carcinoma in these lesions (17 1% during 1936-44)

Clinically it is difficult to distinguish between carcinoma and nontoxic nodular goiter Hoarseness and vocal cord paralysis (besides metastases) are the only manifestations of value in diagnosing carcinoma Sex and age are of slight importance and consistency of the nodule is of no value Vocal cord paralysis was seen in 28 8% of the cases of carcinoma and not at all in benign nontoxic nodular goiter

Treatment of solitary nontoxic nodular goiter is total lobectomy of the involved side including removal of the isthmus if the other lobe is assumed to be normal on actual surgical exploration Multinodular nontoxic goiter should be treated by bilateral subtotal thyroidectomy Total thyroidectomy should be performed for carcinoma of the thyroid with palpable cervical lymph nodes with radical neck dissection in continuity on the affected side

Patients with papillary follicular and alveolar adenocarcinomas have a high five year survival rate whereas those with Hurthle cell giant cell diffuse and squamous cell tumors have a low rate In the literature the five year survival rates for all pathologic types of thyroid carcinoma vary from 7 8% to 71 5% In the present series there was a 36 8% five year survival rate for the 49 patients followed

[The preceding two papers present traditional attitudes toward thyroid nodules based on experience with a huge number of thyroidectomies

(3) J Cl n Endoc 1 13 1530 1541 D embe 1953

It is interesting to note in the second that increasing the number of thyroidectomies for nodular goiter (i e raising the index of suspicion) failed to increase the number of carcinomas discovered Thi suggests (as discussed below) that the riteria u ed for selection of patients for operation during 1936 44 included most of the cancers —Ed]

Adenoma and Carcinoma of the Thyroid Gland George Crile Jr[4] (Cleveland Clinic) considers statistics on the incidence of cancer in nodular goiter unreliable because they are based on a selected group of patients whose goiters have been removed Papillary cancer of the thyroid and its lateral cervical metastases have an extremely slow growth Careful examination of all thyroids removed for Graves disease or multinodular goiter shows that 1 in 200 contains a small sclerosing papillary carcinoma that was not palpable before operation If the gross tumor is removed completely metastases or recurrences are not observed In incomplete operations blood and lymph vessels are opened to invasion by the tumor cells and metastases and local recurrences are common For unilateral lesions involving the upper pole the procedure of choice is complete removal of the isthmus and affected lobe of the thyroid and the nodes of the jugular and carotid chains More extensive lesions require total thyroidectomy without division of the thyroid isthmus (to avoid possible implantation of the tumor) A high wide thyroidectomy incision extending far backward into the posterior triangle on each side is preferred Postoperative irradiation is not necessary when primary operation has been complete This method is preferable to the standard block dissection

Of 24 patients studied 20 had metastases to the cervical lymph nodes and all but 1 lesion was operable Twenty three patients were followed 3 15 years with no local recurrences The only distant metastasis was in a case in which the tumor implanted itself in skin following a needle biopsy

Since multinodular goiter is common and highly malignant cancer of the thyroid is very rare 80% of such growths arising without any history of pre existing goiter prophylactic removal of all multinodular goiters is not advocated There is no demonstrable relation between nodular goiter and papillary cancer of the thyroid All discrete firm thyroid tumors that arouse suspicion of cancer whether they are part of a

(4) N w E gl d J M 249 585 590 Oct 8 1953

multinodular goiter or the only palpable nodule should be removed

In patients over age 40 apparently solitary nodules are usually dominant involutionary ones in a multinodular goiter In patients under age 40 a solitary nodule is apt to be a true epithelial neoplasm Most thyroid cancers in this age group are papillary and with adequate operation the prognosis is good

[If patients thyroidectomized for nodular goiters are a selected group with more cancer than the general population as suggested by Crile the true incidence must be estimated from sources other than the records of surgical clinics In the next two papers Sokal attacks this problem.—Ed.]

Occurrence of Thyroid Cancer Joseph E Sokal[5] (Yale Univ) states that because of great differences of opinion as to the incidence of thyroid cancer a statistical study of the disease was made on the basis of data from clinics tumor registries Armed Forces morbidity reports and cancer surveys mortality statistics official mortality tables and other sources and autopsy statistics from several medical centers

Clinical data on 122 000 cases of cancer disclosed 680 (0 56%) cases of thyroid cancer and the incidence in the various studies ranged from 0 8 to 0 33% In mortality statistics on 378 000 deaths from all kinds of cancer, the incidence for thyroid cancer was 0 405% The average incidence of cancer of the thyroid gland in several series of autopsies averaged 1 1 200 deaths The validity of autopsy data has been denied by several authors who claim that thyroid cancer is much more common than is indicated by autopsy figures as most of its victims do not reach autopsy Available data however indicate that thyroid carcinoma comes to autopsy oftener than most diseases

The aggregate of clinical data and mortality and autopsy statistics indicates a 0 44% incidence of thyroid cancer among all cancer deaths The clinical incidence is somewhat higher than its incidence as a cause of death This is consistent with current experience which indicates that thyroid cancer is more curable on the average than most cancers In a typical community of 1 000 000 persons 25 would have thyroid cancer with one new case appearing monthly Six persons a year would die of thyroid cancer and of them one or two would come to autopsy

(5) New England J Med. 49 393 397 Sept 3 1953

Incidence of Malignancy in Toxic and Nontoxic Nodular Goiter was studied by Joseph E Sokal[6] (Yale Univ) in cases reported in the American literature during the past 25 years A tabulation from various medical centers showed that of 1 803 thyroid cancers 9 6% were associated with hyperthyroidism a disease affecting only about 0 2% of the population In one reported series the material was derived from study of a population with an 60% incidence of adenomatous goiters 15% of which were exophthalmic (autopsy data) In this population nodular thyroids must have been about as common among euthyroids as among those with hyperthyroidism yet almost half the thyroid cancers were associated with hyperthyroidism thus indicating that cancer is more likely to occur in a hyperactive gland other factors being equal

Cancer was found in 0 94% of 5 011 nodular toxic goiters and in 0 15% of 13 868 diffusely hyperplastic toxic glands Nodular goiter occurred in 36% of 12 610 cases of hyperthyroidism Thus in a hypothetical population of 20 000 hyperthyroid patients 7 200 would have nodular thyroids and of these 68 would have cancers Among the 12 800 diffusely hyperplastic glands there would be 19 cancers Since thyroid cancer is at least 20 times as common among hyperthyroid as among euthyroid persons it follows by extrapolation that among 20 000 euthyroid adults there would only be four cancers at most The bulk of thyroid cancer arises in pre existent nodular goiter (three fourths in some series) Therefore three of the four cancers in euthyroid adults belong to persons with thyroid nodules leaving one cancer for those with nongoitrous or diffusely enlarged glands About 8% of an adult population may be expected to have palpable thyroid nodules i e 1 600 of the hypothetical population will have nodular goiter Three (at most) will have cancer and only one cancer will be found among the 18 400 who have no or diffuse goiter

Expressed in terms of total hazard to a person with an average life span cancer of the thyroid will develop in about 0 1% of the population i e in 1 per on/1 000 Not all thyroid cancer arises in pre existent nodules Therefore in less than 1 person/1 000 will cancer develop in a nodular goiter however over 100 persons will have thyroid nodules at some time

(6) J A M A 154 13 1 1325 Ap 17 1954

On this basis the cumulative lifetime risk of cancer developing in a thyroid nodule must be less than 1%. Histologic examination of randomly selected nontoxic nodular goiters would show cancer in no more than 0.2%. This statement is borne out by the report of a leading Chicago thyroid surgeon who saw fewer than five cases a year during 12 years. In a large general hospital in Chicago only three cases a year were seen over 18 years.

Reports that nodular goiter is more dangerous in men than in women are not valid since the data are drawn from a study of unrepresentative samples.

No distinction has been drawn between uni and multinodular gland because not enough statistical data would have been available and clinical differentiation between the two types is subject to great preoperative error.

Treatment of Thyroid Cancer Metastases with TSH and I^{131} during Thyroid Hormone Medication, based on the hypothesis that thyroid hormone suppresses the pituitary while the TSH stimulates the tumor and metastases resulting in increased isotope uptake, was attempted by Charles T. Sturgeon, Fremont E. Davis, Boris Catz, Donald Petit and Paul Starr[7] (Univ. of Southern California).

A study of the life cycle of carcinoma of the thyroid showed that the disease might be present for 22 years before diagnosis was made and it was not uncommon for the patient's condition to be good 10 or more years after the diagnosis. The study included 11 males and 39 females aged 5-78. In six a metastatic lesion was the first sign of cancer. The time between recognition of a mass and pathologic *diagnosis varied* from 7 months to 41 years. Survival time following surgery was 7 months to 25 years. There were 27 patients with papillary, 12 with alveolar and follicular and 11 with other type tumors. The papillary type traveled to the regional lymph nodes then to the lungs, whereas the follicular type spread to the bones and lungs; metastases from the other types were unpredictable.

Hitherto treatment of metastatic thyroid cancer included (1) removal of all thyroid tissue, (2) suppression of iodide uptake by large doses of thiouracil and (3) stimulation by thyrotropic hormone. Because this approach was unsuccessful

(7) J. Cl. E doc. 13 1391 1407 N emb 1953

the following regimen was adopted (1) surgical removal of all accessible thyroid gland and metastases and complete de struction by isotope of inaccessible thyroid tissue (2) x ray survey to locate other metastases (3) thyroid or thyroxin medication to maintain constant euthyroidism as estimated clinically and by determination of serum protein bound iodine concentration (4) tracer studies with radioactive iodine to establish any collection of the isotope in the thyroid or other parts of the body and 72 hour determination of urinary excre tion of the tracer (5) parenteral administration of 15 mg TSH twice daily for six days (6) repetition of tracer studies with isotope to observe improvement in collection or reduc tion in excretion of tracer (7) if significant increase of reten tion is found immediate administration of a therapeutic dose of radioactive iodine (100 mc) and (8) if there is no change in uptake or retention of isotope continued thyroid medica tion and repetition of the study in six months

Of the 50 patients 14 treated with radioactive iodine dur ing induced hypothyroidism showed no evidence of retention of the isotope Under the regimen of maintained euthyroidism by thyroid hormone therapy 4 of 13 patients showed reten tion of a therapeutic dose of radioactive iodine after treatment with thyrotropic hormone

[If TSH stimulates the *gro th* of the cancer as well as its ability to take up I^{131} it is des rable to eliminate endogenous TSH Thi technic may prove to be a considerable improvement ove previous methods depending on the induct on of severe hypothyroidi m with consequent constant endogenous TSH hypersecretion —Ed]

THE ADRENAL GLANDS

Clinical and Metabolic Actions of Aldosterone (Electro cortin) a newly discovered adrenal steroid 18 oxo corticos terone are described by R S Mach J Fabre A Duckert R Borth and P Ducommun[8] (Geneva) in two cases of Addi son s disease When desoxycorticosterone acetate therapy was omitted for 48 hours in one patient great somnolence patho logic fatigue and dyspnea on the least effort developed He complained of lumbago painful weakness of the plantar sur faces of the feet arthralgia of the knees nausea anorexia

(8) S hw m d W b h 84 407 416 Ap 10 1954

hiccups and a sensation of oculonasal swelling Symptoms improved 30 minutes after administration of aldosterone and disappeared entirely in an hour only to reappear at the end of 7 8 hours regardless of dosage used This suggested that the drug should be administered three times daily Improvement in asthenia was demonstrated by an ergogram which showed an increase in the work done under therapy followed by a decrease on withdrawal of medication

Subjectively both patients estimated that aldosterone corrected the manifestations of adrenal insufficiency more effectively than desoxycorticosterone acetate (DCA)

While aldosterone was being given arterial tension was slightly lower than during adrenal insufficiency DCA always caused a marked increase in tension The different effect of the two hormones on vascular tone may have important therapeutic implications Both drugs permitted development of orthostatic hypertension the absence of which is characteristic of adrenal insufficiency

After six days of therapy with aldosterone skin depigmentation was greater than when cortisone was administered for several months The depigmentation remained for two weeks after therapy was discontinued

Under aldosterone sodium and chloride were retained whereas potassium excretion increased Thus in one patient the negative sodium and chloride balance during insufficiency became positive when aldosterone was given Potassium balance was on an average plus 34 mEq without therapy and only plus 16 mEq /day under treatment The effect was similar to that obtained with DCA

During the first three days of therapy one patient gained slightly over 1 lb the increase was due in large measure to a nitrogen gain corresponding to the formation of 280 Gm protoplasm and water retention of about 200 cc Simultaneously there occurred an increase in plasma volume estimated at 470 cc and an increase in extracellular fluid to about 780 cc three fourths of the latter being due to displacement of cellular fluid

The effect of aldosterone on electrolyte metabolism was evident within three to six hours Hemodilution reached its maximum in 24 hours and sodium loss or hemoconcentration appeared on the following day Aldosterone seemed to act like

DCA on the distal tubules of the kidney in favoring reabsorption of Na and excretion of K and H ions Calcium and phosphorus balances were unchanged

Aldosterone caused normalization of the blood sugar curves in the oral glucose tolerance test The hyperglycemic peak was increased and the hypoglycemic reaction suppressed

There was no retention of nonprotein nitrogen such as was reported in dogs when DCA was replaced by the natural hormone There were no significant changes in total fat total cholesterol or cholesterol esters under therapy The result of the water test was not improved with aldosterone There was no decrease at any time in the eosinophil count or significant changes in the formed elements of the blood while the drug was administered

In one patient there was unquestionable improvement in arthralgia The drug had no effect on temperature or sedimentation rate and no important changes occurred in the 17 ketosteroid and (formaldehydogenic) corticoid levels in the urine

The effective dosage of aldosterone varied between 150 and 200 μg /day (2 5 3 3 μg /kg) Thus the potency is 20 30 times greater than that of DCA However unlike DCA aldosterone did not seem to cause elevated blood pressure or pathologic water retention

[These initial studies in human subjects show that aldosterone (electrocortin) by far the most potent electrolyte controlling adrenal steroid has a blood pressure regulating effect different from DCA (which is probably not a natural adrenal steroid) Its effects on arthralgia and carbohydrate and pigment metabolism are unexpectedly like those of hydrocortisone but it differs from this steroid in its lack of eosinopenic and anti anabolic properties —Ed]

Adrenal Response to ACTH in Various Clinical Conditions was determined by Douglas Gordon Benjamin N Horwitt and Albert Segaloff[9] (Tulane Univ) in 27 patients Urinary 17 ketosteroids formaldehydogenic corticoids uric acid/creatinine ratios and total eosinophils were measured over 48 hours An intramuscular dose of 25 mg ACTH was given at 8 a m beginning at 4 p m 10 mg was given every six hours for seven doses If at least two of four determinations showed significant changes the response was considered positive A > 50% increase over the control level of urinary formaldehydogenic corticoid or 17 ketosteroid excretion and a > 50%

(9) J Cl E doc 1 14 97 308 M h 1954

decrease in total blood eosinophils and in uric acid/creatinine ratio are all believed indicative of a significant adrenal response Analyses of 24 positive responses to ACTH is shown in the table In some patients a dissociated type of response was obtained whereby some finding indicated a good response when the others showed no change

Of four patients with breast cancer eosinophil count decreased to zero formaldehydogenic corticoids and uric acid/creatinine ratio both rose but 17 ketosteroids showed little change in one good formaldehydogenic and uric acid/creatinine ratio changes but delayed eosinophil and 17 ketosteroid responses occurred in the second delayed eosinophil response good 17 ketosteroid response but poor formaldehydogenic corticoid and uric acid/creatinine changes were noted in the third and increases in 17 ketosteroids and formaldehydogenic corticoids delayed eosinopenia and little or no change in uric acid/creatinine ratio was observed in the fourth

ANALYSIS OF 24 POSITIVE RESPONSES TO 48 HOUR ACTH TESTS*

DETERMINATION	NO OF SIGNIFICANT RESPONSES	% OF TOTAL
Formaldehydogenic corticoids	22	92
Eosinophils	20	83
17 Ketosteroids	19	79
Uric acid/creatinine	11	46

* Results were considered positive if two or more determinations showed significant changes

A patient with Addison s disease had practically no change in all four determinations A patient with panhypopituitarism had negative results in the 4 hour ACTH test but positive results in the 48 hour test as measured by the eosinophil and 17 ketosteroid response but not by the formaldehydogenic corticoid and uric acid/creatinine changes In two patients with thyroid myxedema adrenal responsiveness was similar to that seen in pituitary failure rather than in primary adrenal failure This indicates that depression of adrenal function in myxedema is probably due to depressed release of ACTH from the pituitary *rather than decreased adrenal responsive*ness In a patient with Cushing s syndrome due to bilateral adrenal hyperplasia 17 ketosteroid and formaldehydogenic corticoid levels were elevated and showed *tremendous in*creases after ACTH significant eosinophil response but no

uric acid/creatinine response After surgery there was a good eosinophil response delayed 17 ketosteroid response and no other changes

After ACTH the most sensitive were the formaldehydogenic corticoid changes and the least sensitive the uric acid/creatinine change Studies in a normal man with and without ACTH administration showed that the spontaneous variation was similar to the ACTH effect This suggests that the adrenal response may or may not be due to the exogenous ACTH alone

[With the adrenal as with other organs several testing technics are better than one —Ed]

Quantitative Evaluation of Primary Adrenal Cortical Deficiency in Man It seemed likely to A Gorman Hills George D Webster Jr Otto Rosenthal F Curtis Dohan Edwin M Richardson Harold A Zintel and William A Jeffers[1] (Univ of Pennsylvania) that while a positive response to corticotropin would indicate the presence of sufficient adrenal tissue to provide some degree of functional reserve lesser amounts of adrenal function might well be separated into several grades corresponding anatomically to (1) a small adrenal remnant constantly under near maximal stimulation and secreting inadequate or scarcely adequate quantities of hormone and (2) a vanishingly small quantity of functioning adrenal cortical tissue A twofold test was devised for a quantitative appraisal of adrenal cortical functional capacity consisting of (1) a standard metabolic regimen capable of provoking acute adrenal insufficiency in the patient with severe adrenal deficiency and (2) powerful adrenal cortical stimulation by *intravenous administration of corticotropin*

Study of nine patients who had undergone subtotal adrenalectomy because of severe hypertensive vascular disease and six with normal adrenals revealed that patients could be classified into one of four separate grades of adrenal cortical functional capacity on the basis of multiple criteria of response to each portion of the test Grade 0 indicates acorticism with no reserve grade 1 cortical inadequacy with no reserve grade 2 hypocorticism with reduced reserve and grade 3 eucorticism with large reserve During the provocative test grade 0 patients have signs and symptoms of ortho

(1) Am J M d 16 3 8 339 M b 1954

static faintness, usually with tachycardia and hyperpnea and lassitude weakness anorexia nausea or vomiting all becoming increasingly severe Grade 1 patients have these same symptoms during the first 24-48 hours but without further progression or with amelioration on the 7th and 8th days of the study Grade 2 and 3 patients have no signs or symptoms of adrenal insufficiency In grade 0 the serum sodium level *falls to 128 mEq /L or below and the serum potassium level* rises to 6 2 mEq /L or more in grade 1 serum urea rises to the total extent of 20% Electrolyte balance studies in grade 0 reveal negative mean daily balance of sodium with a more negative balance during the corticotropin test in grade 1 a negative mean daily sodium balance during the provocation and corticotropin tests but less so during the former in grades 2 and 3 a positive sodium balance during the corticotropin test When florid adrenal crisis requiring interruption of the test is attended by grade 0 change of serum electrolytes the final grade is 0 the corticotropin test is not needed In grade 0 and 1 there are a positive potassium balance during the corticotropin test and a mean daily balance during the provocation test of + 10 mEq or more In grades 2 and 3 potassium balance is negative during the corticotropin test and the mean daily balance during the provocation test is less than + 10 mEq

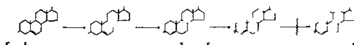
In grades 0 1 and 2 there is an eosinophil decrease of less than 90% at the end of the corticotropin infusion and in grade 3 a decrease of circulating eosinophils of 90% or more

A base line value is calculated for each type of urinary steroid and this is then averaged to obtain the mean base line value for all types of steroid measured This mean is compared with the mean of the 24 hour excretion of the three types of steroid during the corticotropin test The change is an index of adrenal responsiveness to corticotropin and is graded as *follows grade 0 or 1 no change or a mean decrement* grade 2 a mean increment of 4 mg or less/24 hours and grade 3 a mean increment greater than 4 mg /24 hours

Studies on Metabolism of Adrenal Steroids in Adrenogenital Syndrome are reported by Alfred M Bongiovanni

Walter R Eberlein and Jose Cara (Johns Hopkins Univ) In 13 patients with adrenogenital syndrome due to adrenocortical hyperplasia the level of pregnanediol in the urine was elevated as high as 2 4–118 mg /24 hours and after cortisone treatment for two days to one month it dropped to 0 6 9 mg / 24 hours In these patients there was chromatographic evidence that the material in the urine considered to be pregnanediol was primarily pregnanetriol Pregnanetriol probably represents a metabolite of 17 hydroxyprogesterone reflecting a defect in synthesis of compound F in this disease

In seven of nine patients treated with 0 5 mg corticotro







Fg 101 —(C t y f B g ov A M t / J Cl E doc 1 14 409 422 Ap 1 1954)

pin/kg intravenously over three to four hours the low levels of blood corticoids failed to rise normally Since two patients showed satisfactory response to adrenocortical stimulation the defect in biosynthesis may not be complete

The excretion of pregnanetriol like that of 17 ketosteroids is suppressed by administration of cortisone but rapidly reappears following administration of corticotropin (for short periods) or of 17 hydroxyprogesterone Its presence may aid in diagnosis when 17 ketosteroid levels are low

The study provides additional information on the defect in biosynthesis of the corticoids in the adrenogenital syndrome Hechter proposed a schema for the biosynthesis of 17 hy

(2) J Cl E docn 1 14 409 422 Ap 1 1954

droxycorticosterone (compound F) by the adrenal gland The last step involves the conversion of 17 hydroxyprogesterone into compound F (Fig 101) Progesterone is also an intermediary metabolite in the synthesis of compound F from cholesterol Pregnanediol is a metabolite of progesterone Pregnanetriol is a metabolite of 17 hydroxyprogesterone and in the adrenogenital syndrome there is a block in the conversion of 17 hydroxyprogesterone into compound F It is unlikely that pregnanetriol per se is androgenic because 17 hydroxyprogesterone was not detected in the blood of patients studied There is no definite knowledge that 17 hydroxyprogesterone is converted into other steroids which have androgenic activity A large proportion of the 17 ketosteroids in the urine of patients with adrenal hyperplasia are of the 11 oxygenated type It is improbable that these represent products of 17 hydroxyprogesterone

Hormone Patterns in Patients with Congenital Adrenal Hyperplasia Vincent C Kelley Robert S Ely and Richard B Raile[3] (Univ of Utah) studied seven children with female pseudohermaphroditism and one with macrogenitosomia praecox both conditions due to congenital adrenal hyperplasia One case of male pseudohermaphroditism was added for comparison The eight with congenital adrenal hyperplasia were given 12 5 50 mg/day cortisone intramuscularly or orally 25 I U of corticotropin intramuscularly was also given to most patients to test 17 hydroxycorticosteroid response

Measurements were made of plasma 17 hydroxycorticosteroid concentration urinary 17 ketosteroid excretion and corticotropin titers before and after cortisone administration Before therapy endogenous corticotropin concentrations and 17 ketosteroid excretion were abnormally high and circulating 17 hydroxycorticosteroid levels low During cortisone therapy these values approached normal

The adrenal cortex responds to circulating corticotropin by producing androgen precursors Only small amounts of 17 hydroxycorticosteroids the normal inhibitors of corticotropin secretion are produced and are insufficient to inhibit excessive corticotropin secretion This increases the stimulation of the adrenal cortex and in turn excessive production of androgen

(3) Pediatrics 12 541 548 November 1953

precursors without a corresponding increase in 17 hydroxy corticosteroid production This results in elevated concentrations of endogenous circulating corticotropin elevated urinary excretion values of 17 ketosteroids and low concentrations of circulating 17 hydroxycorticosteroids The adrenal cortex of the child with congenital adrenal hyperplasia cannot respond to injected corticotropin by elevation of 17 hydroxycorticosteroid level therefore it is presumed that the primary abnormality resides in the adrenal cortex

The corticotropin 17 hydroxycorticosteroid response test is an additional chemical technic for differentiating female from male pseudohermaphroditism In the male type there is no adrenal dysfunction and both 17 ketosteroid excretion and the corticotropin 17 hydroxycorticosteroid response are normal The plasma 17 hydroxycorticosteroid response test is applicable in early infancy and therefore permits differentiation even before 17 ketosteroid excretion becomes abnormal

[The preceding two papers strongly support the thesis that the adrenogenital syndrome results when the adrenal cortex is partially or totally unable to convert 17 hydroxyprogesterone to hydrocortisone The increased corticotropin secretion resulting from this partial or total adrenocortical failure stimulates overproduction of both 17 hydroxyprogesterone and adrenal androgens Although the full blown masculinizing picture is easily recognized one wonders whether formes frustes of this biochemical lesion may be responsible for occasional cases of sterility as in the following report This possibility has also been discussed by Jones *et al* (Fertil & Steril 4 49 January 1953) —Ed]

Conception during Cortisone Therapy and Effect on Offspring A case is reported by Harry G Kupperman[4] (New York Univ)

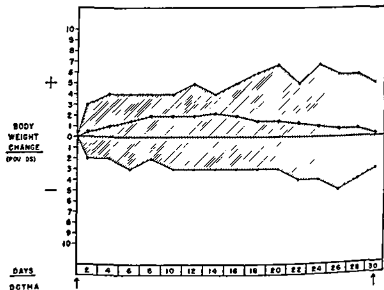
Woman 22 was treated with cortisone one year after trauma to her right arm which produced a flexion contracture She received 200 mg cortisone the first two days and 100 mg daily thereafter for a total of 3 Gm in two months She improved temporarily but had moon face bilateral pretibial edema oligomenorrhea and gained 10 lb There was no glycosuria or hypertension Amenorrhea for two period was attributed to the cortisone therapy but further examination showed a 2½ month pregnancy The cortisone had been started on the first day of her last menstruation Apparently she conceived while on therapeutic doses of cortisone which did not interfere with the progress of the pregnancy or have any effect on the offspring

She was sterile for six years of her married life The first pregnancy was followed by miscarriage The possibility that

(4) New York J M 53 3033 D 15 1953

cortisone may have a favorable effect on sterility or pregnancy in instances of hormonal imbalance merits further investigation

Use of Desoxycorticosterone Trimethylacetate in Treatment of Addison's Disease George W Thorn Dalton Jenkins Walter L Arons and Thomas F Frawley[5] (Harvard Med School) report a study of 45 patients treated for six months or longer Before treatment with desoxycorticosterone tri



F g 10 —S mmary of 100 body w ght h rt from 35 p t ent w th Add son s d sea e rece : g d s xycort cost on t m thyl t te at 30 d y ter al Shaded are dem cate m im l h g n w ght e h b t d by th nt group m n body we ght ch ge al o h w (Cou te y of Tho G W et l J Cl n Endoc nol 13 957 973 A gu t 1953)

methylacetate (DCTMA) 37 patients had desoxycorticosterone acetate (DCA) pellet implantations and 8 had daily injections of DCA in oil

In Addison s disease weight gain accompanies improvement and weight loss indicates a relapse Change in weight is therefore a sensitive index of clinical status and efficiency of a drug A composite of 100 weight charts collected from 35 patients each chart including a 30 day period between injec

(5) J Cl n E doc n l 13 957 973 A gust 1953

tions is shown in Figure 102 The maximal limits of weight gain and loss are a reflection of over or under dosage After the first month 90% had a weight change of less than 5 lb and 80% varied 3 lb or less from the initial weight

The effect of trimethylacetate on electrolyte excretion (sodium chloride and potassium) by the kidneys is the same as that of DCA In 28 patients with Addison s disease and 2 with carcinoma of the prostate who had orchiectomy and complete bilateral adrenalectomy there was excellent control of hydration electrolyte balance and cardiovascular function

SUMMARY OF DOSES ADMINISTERED AT 30 DAY INTERVALS TO 45 PATIENTS

DCTMA Do M	PA NTS
15	2
30	7
45	7
60	20
90	9

Most patients were able to return to work after treatment One patient recently delivered a normal infant following an uneventful pregnancy

The preparation used in this study was DCTMA in isotonic saline containing up to 1 3% methylcellulose and 0 1% tween® 20 as suspending agents and merthiolate® (1 50 000) as a preservative The drug was administered intramuscularly in amounts previously determined for DCA at 30 day intervals A single 30 mg dose resulted in a daily absorption of 0 6 1 mg For each milligram of DCA injected daily 30 mg (1 ml) DCTMA suspension was injected at 30 day intervals or 15 mg of the suspension was substituted for each pellet required A summary of doses given at 30 day intervals to 45 patients is shown in the table

The potential side effects are those found with any desoxy corticosterone preparation There were four pyrogenic reactions which are being investigated

Cushing s Syndrome is discussed by Abbie I Knowlton[6] (Columbia Univ) on the basis of 33 patients treated at the hospital and 189 cases from the literature Obesity is the hallmark of the syndrome In each instance whether the patient gained or lost weight there was redistribution of tissue

(6) B ll N w Y k Acad Med 29 441 465 J 1953

to give the characteristic facial and truncal obesity Painful obesity was relatively unusual Hypertension with high diastolic levels was common (Table 1) and was completely reversible in patients who had remissions Funduscopic changes were noted in only 5 of 34 patients who had eyeground examinations Gonadal function was usually suppressed but virilization was rare this distinguishes Cushing's syndrome from adrenogenital syndrome Enlargement of the clitoris was seen

TABLE 1 —SYMPTOMS AND SIGNS FREQUENTLY ENCOUNTERED IN CUSHINGS SYNDROME

	Col mbia S ries (38 p tie t)	Rep l f om l terat e (189 p t ent)
	per ce t	p r ent
Obes ty — tr l l f l	95	9
pl thori pp	85	50
d rmatol gi l b rm l t es	8	26
Hyperten on	9	85
D st b go d l f ct m n h ol gom or rhe mpot ce	66	1
virl m	6	5
Hirs t m	76	69
P rple st	69	71
Weakn nd back ch	68	50
M nt l b o mal t s	66	31
m r 40		
m j 6		
P rp easy bru g	58	93
Poor wound h ling or e f t	4	30
He d ch	40	34

in only two patients of the series None had masculine voice or body configuration but most had hirsutism Two patients were pregnant while the disease was progressing There were frequent abnormal mental reactions ranging from emotional lability to major disturbances in 26% of the patients including depressions paranoid reactions and confused states One attempted suicide There was uniform clearing of the mental picture during remission A significant number of patients had severe and protracted headaches but no correlation existed between them and other neurologic signs and symptoms One patient with a basophilic adenoma and two with chromophobe adenoma were without headaches whereas this

TABLE 2—RELATION BETWEEN PITUITARY AND ADRENAL LESIONS (97 AUTOPSIES)

	Ad enal F nd gs						
P tuit y F ndi g	Hyperplasia f ad en ls	C m f d nal	L lat al tum r phy f pp d	H m rrh ...	Hypoplasia f ad en l	N rmal d	T t l
Crooke's hy l izat w th t th pit itary b rm lity	17	11	5			1	34
B sophil den m	4		1	2	1	3	31
I c eased mbe b ph l b soph l in f p t l b	4	1	1			2	8
Mi ed basoph li hrom ph b d na	3						3
Ch moph b ad ma	5	1				1	7
Mi d hrom ph b -eo phil d ma	1						1
E inopl l denom	1	1					2
I d mb ophil		1					1
U pecifi d d om	1		1			1	3
Atrophy d fib	1						1
Sca dest y g ohypophy s d p s t rm d s						1	1
N rm l	1		3				6
T t l	58	17	11		1	9	98

I l d w se h l l hyp phy f d al w hou l mor

TABLE 3—ADRENAL OPERATIONS IN CUSHING'S SYNDROME

	T t l	U h g d	Sl. mp	Cur d	D d
R m l be gn d en l d m	6			3	3
E pl t f d l	2	1			1
B p y d p rt l ectio f b th d l f hyp rpl	10	10			
S bt t l d l ct f l p jl			2		
R mo l d l m	2		1		2

Imp m l m h

symptom was particularly severe in four patients with adrenal tumors

Few laboratory findings were abnormal consistently enough to help in diagnosis There was a diminished tolerance to car bohydrates and a small percentage had frank diabetes The over all average fasting blood sugar was normal There was

no instance of diabetic acidosis in the author's patients only one such instance was recorded in the 189 cases in the literature Excretion of 17 ketosteroids was normal on the average in Knowlton's group *Demineralization of the spine* was present in 74% Serum values of electrolytes were usually normal

The extraordinary variety of adrenal and pituitary pathology which has been reported in Cushing's syndrome is seen in Table 2 The most frequent combination is hyperplasia of the adrenals with a basophilic adenoma of the pituitary

Therapy must vary with the underlying pathology and the presence of a pituitary or adrenal tumor should be determined Types of adrenal operations are shown in *Table 3* Pituitary irradiation was carried out in 20 patients 10 of whom had some degree of remission No correlation was noted between the dose and duration of therapy and improvement The main cause of death was infection The second major cause of death was cardiovascular disease (cardiac failure cerebrovascular accidents and uremia)

Effect of Cortisone on Urinary Excretion of 17-Ketosteroids in Patients with Cushing's Syndrome Joseph W Jailer Jean Louchart Jay J Gold and A I Knowlton[7] (Columbia Univ) injected 200 mg cortisone intramuscularly daily for four or more days in each of five patients with proved adrenal hyperplasia In all five patients 17 ketosteroid excretion declined significantly In one patient 17 ketosteroids declined only 25% after cortisone administration however a second test with cortisone six months later produced an impressive reduction in 17 ketosteroid excretion In another patient the decline was from a high of 14 3 before cortisone administration to 3 6 after completion of the experiment No deleterious effects on any patients were noted Administration of 200 mg/day cortisone to a normal subject resulted in a 40% decline in the total neutral 17 ketosteroids

In a patient with Cushing's syndrome due to adrenal carcinoma the control values of 17 ketosteroid excretion were elevated The administration of 100 mg of cortisone intramuscularly daily for four days was without demonstrable effect on the 17 ketosteroid output Apparently the tumor in *this* patient was autonomous and unlike normal or hyperplastic adrenal tissue was not under pituitary control Hence

(7) J Clin. Invest. 48 449-452 May 1953

pituitary inhibition as achieved by cortisone administration was without effect on the secretion of 17 ketosteroid pre cursors This was further borne out by the fact that following complete hypophysectomy the level of urinary 17 ketosteroids and the clinical course remained unchanged

These findings provide evidence for the speculation that the hyperplastic adrenal glands in Cushing s syndrome remain under pituitary control since when ACTH secretion is sup pressed by cortisone the concomitant fall in urinary 17 ketosteroid secretion reflects decreased cortical activity

If suppression of adrenocortical activity occurs as a result of exogenous cortisone administration and there is a resultant decline in the urinary 17 ketosteroid level the adrenal must be secreting other 17 ketosteroid precursors be sides cortisone and compound F It is possible that the adrenal contribution to the 17 ketosteroids includes an androgen As say of cow adrenal vein blood by other investigators has demonstrated the existence of an adrenal androgen

[Jailer has previously demonstrated the usefulness of the cortisone test for differentiating hyperplasia from tumor as a cau e of the adreno-genital syndrome (J A M A 150 575 195?) In thi d sease as in Cush ing's syndrome the corti one test may avoid unnecessary surgical ex ploration to determine the pathologic process The test works because adrenal tumors function independently of endogenous corticotropin as shown in the next report —Ed]

Lack of Effect of Hypophysectomy on Metastatic Adreno cortical Carcinoma with Cushing s Syndrome Abbie I Knowl ton James Lawrence Pool and Joseph W Jailer[8] (Presbyte rian Hosp New York City) report a case

Man 26 had a typical history and laboratory and physical find ings of Cushing s syndrome An adrenocortical carcinoma was re moved He did well for a few weeks but soon had evidence of metastases to the vertebrae liver and lungs as well as diabetes which required up to 80 units of insulin/day for control of glyco suria He excreted large quantities of 11 keto etiocholanolone a degradation product of cortisone or 17 hydroxycorticosterone Two months after adrenal surgery hypophysectomy was undertaken in the hope (1) that growth of the neoplasm might like that of normal adrenal tissue in some measure be dependent on the endogenous production of corticotropin and/or (2) that the operation might non specifically inhibit tumor growth

No significant change in the clinical picture occurred after opera tion except the appearance of a state resembling mild diabetes insipidus No steroid replacement therapy was given after the first

(8) J Cl E docri l 14 05 14 F bru ry 1954

postoperative week Nevertheless the severe diabetes mellitus normal serum electrolytes or values suggesting hypochloremic alkalosis greatly elevated urinary excretion of 17 ketosteroids and corticoid and a pre existing psychosis all persisted essentially unchanged

The patient s condition deteriorated after hypophysectomy and he died seven weeks later Autopsy revealed widespread malignant metastatic disease and moderate atrophy of the thyroid testes and remaining adrenal gland No pituitary tissue was found

Prevention of ACTH Induced Sodium Retention by Use of Potassium Salts A Quantitative Study is presented by Grant W Liddle Leslie L Bennett and Peter H Forsham[9] (Univ of California) Seven men and seven women with various afflictions were studied Throughout the 30 experiments of the study a constant diet was maintained total urine output was collected and specimens of feces saliva and blood were taken for electrolyte determination ACTH was given intramuscularly and cortisone acetate or hydrocortisone orally in four divided doses daily Potassium was administered orally in small divided doses and in a few cases it was given by continuous intravenous infusion

Oral administration of large doses of either potassium chloride or potassium acetate consistently resulted in a diuresis of sodium The degree of sodium diuresis was greater in subjects in whom sodium retention was induced by ACTH or cortisone than in untreated subjects The administration of potassium chloride and potassium acetate resulted in a decrease of urinary phosphate ammonia and titratable acid and an increase in urinary bicarbonate and chloride The increase in sodium was proportionately much greater than the increase in chloride Neutral potassium phosphate administered intravenously caused sodium and chloride diuresis without causing a decrease in urinary titratable acid plus ammonia

Two possible mechanisms may account for the natriuretic effect of potassium salts (1) displacement of body Na^+ by K^+ and (2) suppression of renal tubular H^+ Na^+ exchange Sodium retention and potassium depletion are clinically significant only when cortisone or ACTH is given in relatively large doses i e 100 mg or more daily for more than one week When doses greater than this are given and dietary salt is not restricted a potassium supplement of 200 mEq /day or more is sufficient to prevent sodium retention Although po

(9) J Cl In st. 32 1197 1207 Decembe 1953

tassium in this dosage frequently causes abdominal cramps or nausea in untreated subjects even larger amounts are usually well tolerated by subjects receiving corticoid therapy It is best to give the daily amount of potassium in divided doses

Psychiatric Risk from Corticotropin and Cortisone Aubrey Lewis and J J Fleminger[1] (London) administered cortisone or corticotropin to 11 patients with rheumatoid arthritis and 1 patient with disseminated lupus erythematosus all of whom had a history of recent mental illness These illnesses included obsessional neurosis gross conversion hysteria schizophrenia involutional depression and acute anxiety state the most common being depression All patients received a placebo before and after hormone therapy Average total amount of corticotropin administered was 2 680 mg and of cortisone 5 560 mg Average duration of corticotropin therapy was 5½ weeks and of cortisone therapy 7½ weeks

All patients showed some physical improvement during therapy On completion of therapy eight were better than before treatment and two were worse In none of the patients was there any definite change in mental state during the placebo administration and in none did severe mental illness develop during hormone treatment Such mental changes as occurred could be accounted for as responses normal or hysterical to changes in physical symptoms or as minor fluctuations in the mental disturbances which they had had before treatment Mental benefit during treatment paralleled physical improvement As pain and disability lessened so did the patients pessimism stoical reserve or resigned gloom clear up The mental improvement was an understandable psychologic reaction and not a direct pharmacologic effect

While receiving doses as high as 100 mg or more/day three patients were irritable and another became extremely restless

Psychologic tests showed no decisive evidence of cognitive or emotional changes when the findings before treatment were compared with those obtained at the height of treatment with the maximal dose of hormone

It is concluded that patients with unstable neurotic personality or a history of mental illness cannot be assumed to have a predisposition to untoward mental symptoms under

(1) Lan t 1 383 386 F b 20 1954

treatment with corticotropin or cortisone Psychotic episodes do occasionally occur in patients receiving these hormones Whatever determines their occurrence is hardly likely to be the same hereditary or environmental constellation inferred from a history of previous mental illness High doses and prolonged treatment may be important factors in development of mental symptoms but psychosis has occurred often in patients receiving small doses thus indicating that other factors are involved

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THE PITUITARY GLAND AND BRAIN STEM

Endocrine and Other Clinical Manifestations of Hypothalamic Disease Survey of 60 Cases, with Autopsies is reported by Hans G Bauer[2] (New York Med College) In the 40 males and 20 females studied there were 51 neoplasms 7 inflammatory and 2 degenerative lesions Six patients had complete destruction of the hypothalamus 35 had destruction of between one third and two thirds and 11 less than one third Extent of involvement did not necessarily parallel degree of functional change The average number of hypothalamic linked symptoms was three per patient Lesions of the floor of the 3d ventricle gave rise to more symptomatology than those of the walls or the roof The mathematical average of hypothalamic symptoms resulting from lesions of the floor of the 3d ventricle was 4 2 In lesions of the walls or roof of the 3d ventricle the average was 2 3

Modification of sexual function and development was the most frequent sign of hypothalamic involvement (43 of 60 patients) and was a presenting symptom in 21 But in 33 of 35 patients the pituitary was normal on gross examination proving that marked alteration of sexual function may be caused by hypothalamic pathology per se Precocious puberty occurred in 19 males and 5 females all with normal pituitaries Hypogonadism occurred in 12 males and 7 females Eight patients with hypogonadism had a craniopharyngioma but there were 14 craniopharyngiomas not associated with precocious puberty Accelerated bone growth usually accompanied precocious puberty

Diabetes insipidus was the second most frequent sign but

(2) J Clin Endocrin 1 14 13 31 J   ry 1954

was a presenting symptom in only two Psychic disturbances were just as frequent as diabetes insipidus and were the presenting symptoms in 7 patients whereas somnolence occurred in 18 and was the first symptom in 6 Obesity occurred in 15 patients emaciation in 11 both were late in appearing Six patients had unexplained fever and seven had subnormal temperatures (below 90 F) Eye signs were present in 47 patients but in only 8 were they the presenting sign The statement that eye signs are of no value in localizing lesions is based on inadequate neuro ophthalmologic examinations Pyramidal and sensory nerve disturbances occurred in 45 patients but headaches and vomiting as symptoms of brain tumor were rare The glucose tolerance test is important in demonstrating disturbances in glucose metabolism although only one patient had glycosuria

In 52 patients with a tentative diagnosis of brain tumor the correct diagnosis was missed in 31 in 6 even an air ventriculogram was of no help Laparotomy was performed on five patients in an attempt to locate an endocrine lesion in the adrenals or ovaries Suboccipital craniotomy was performed on three patients but no tumor of the posterior fossa was found In patients with hypothalamic symptoms and cerebellar symptomatology the hypothalamus as the seat of the lesion should be considered first in the absence of internal hydrocephalus

Hypopituitarism and Some Disturbances of Consciousness Associated with It are described by J E Caughey[3] (Otago New Zealand) in 12 patients

Case 1—Woman 50 had advanced hypopituitari m following septicemia at the birth of a stillborn child After any infection she could sleep the clock round twice and go without food for two days On admission she was in coma pale and dehydrated Blood pressure was 80/55 and the pulse rate 60/minute Her skin was puffy the head and eyebrow hair was scanty and she had no other body hair The cerebrospinal fluid was normal Improvement occurred within 24 hours on 10 units corticotropin intravenously twice daily This was continued for 14 days Testosterone 400 mg and desoxycorticosterone acetate 100 mg were implanted and thyroid was administered orally She made good progress On one occasion injection of ¼ gr morphine sulfate resulted in a two day coma

Case 11—Man 46 had a chromophobe adenoma of the pituitary with bitemporal hemianopsia and hypopituitari m Recovery from

(3) A t 1 An M d 3 26 36 F bru y 1954

the operation was incomplete with disorientation confusion and incontinence of urine and feces 36 hours after Although it appeared to be a crisis of hypopituitarism postoperative hemorrhage could not be excluded Therefore the frontal flap was turned down and a small clot removed He failed to rouse and the procedure was repeated Cortisone 100 mg intramuscularly and neo synephrine® 0 5 cc every 6 hours were given with notable improvement in 48 hours

Hypopituitary coma in the patients observed usually followed stress though in some it appeared gradually In four it followed craniotomy in six a febrile illness and in one an injection of morphine Anesthesia nembutal® pentothal® sodium cold weather and flying were precipitating causes The degree of consciousness varied from drowsiness to coma The patients lay quietly with normal pulse rate and a low blood pressure All superficial and deep reflexes were usually present Incontinence of urine and feces occurred in all There was complete amnesia for the duration of coma

Patients with hypopituitarism are unduly susceptible to attacks of hypoglycemia which should be treated promptly with glucose intravenously If the coma has been prolonged the addition of cortisone may prevent development of hypopituitary coma Two of the patients were given corticotropin with good results but in general cortisone would seem to be the hormone of choice Implantation of testosterone and thyroid extract orally should be used as maintenance therapy

[Although hypopituitary patients may appear to have normal adrenal function in ordinary circumstances acute trauma may precipitate evidence of adrenal failure The prophylactic use of cortisone can prevent most of these episodes —Ed]

Oral Cortisone Treatment of Hypopituitarism H L Sheehan and V K Summers[4] (Liverpool) administered small doses of cortisone orally for about two years to three women with severe hypopituitarism due to postpartum necrosis and to one man with hypopituitarism of unknown etiology Thyroid substance had been given earlier with neither beneficial nor harmful effects The initial dose was 12 5 mg daily for one or two weeks then 25 50 mg daily for one to four weeks later gradually reduced to 12 5 mg daily as a maintenance dose Insomnia occurred with doses of 25 and 37 5 mg a day

In all cases the general condition improved strikingly within three or four days The patients became mentally alert

(4) B M J 1 7 3726 M 2 1954

and took a normal interest in their surroundings The initial period of treatment with 25 mg produced a normal capillary flush of cheeks return of axillary secretion and sweating on exercise in all patients this improvement was maintained also on the 12 5 mg /day dosage Two women had no change in body hair but a small amount of pubic hair and some thickening of the head hair developed in one after six months treatment The man who had been impotent before therapy had normal erections and coitus without emissions on a maintenance dose of 25 mg daily Two patients had definite increases in weight

Three patients had increased urinary output during treat ment and two had increased diuresis during the Kepler water diuresis test No increase in urinary nitrogen excretion was noted All had increased output of 17 ketosteroids from a pre treatment level of 0 2 1 0 mg /day to 2 1 2 8 mg during treat ment No significant change occurred in the serum chemistry The serum sodium level remained at about the low range usual in these patients (122 130 mEq /L) and the serum po tassium level fluctuated between 4 3 and 5 1 mEq /L There was no significant alteration in the sensitivity to insulin but the patients commonly showed some improvement in response to hypoglycemia

In three patients cortisone therapy was stopped for three months after about nine months of treatment and all had a gradual but progressive deterioration in the clinical state

Cortisone has been found superior to testosterone in hypo pituitarism except that testosterone restores body hair Use of the drugs together has not produced any definite additive effect apart from that on the body hair

In the long term treatment of hypopituitarism cortisone in a dose of 12 5 mg /day appears adequate for maintenance

Chronic Hyperosmolarity of the Body Fluids with a Cere bral Lesion Causing Diabetes Insipidus and Anterior Pitui tary Insufficiency in a patient is described by William W Engstrom and Albert Liebman[7] (Marquette Univ)

Woman 28 had bled severely after the birth of her first child Amenorrhea began after the second delivery and four years later severe thirst and polyuria developed She complained that she drank at least 2 pails of water every 24 hours and was up half

(7) Am J M d 15 180 186 A gu t 953

the night drinking and urinating She would lapse at times into sleepy stupor No axillary and scant pubic hair were noted Blood pressure was 78/68 mm Hg in recumbency and unobtainable erect The hands were slightly puffy and the breasts mildly atrophic Visual fields were normal BMR was —27% Results of the Robinson Power Kepler water test (part I) were strongly suggestive (night volume 435 ml and largest day volume 80 ml) Four hours after 25 mg corticotropin was given circulating eosinophils numbered 260 (initially 240) Output of 17 ketosteroids was 2 0 mg/24 hours After two intervals of severe dehydration the specific gravity of the urine was 1 007 and 1 008 Four years later serum sodium level was 161 mEq and of chloride 116 mEq/L Repeated studies when posterior pituitary substance was not being given disclosed serum sodium levels ranging between 150 and 165 mEq and serum chloride levels between 110 and 120 mEq/L

Two other patients with uncomplicated diabetes insipidus were also studied in them pitressin® therapy decreased the voluntary intake of fluid as urinary output decreased whereas in the case summarized the patient with a cerebral lesion drank constant volumes of fluid despite medication The clinical and laboratory evidence in this patient pointed to anterior pituitary insufficiency which according to claims made has a beneficial effect on diabetes insipidus

The hypertonicity of body fluids was alleviated with pitressin® therapy After the withdrawal of pitressin® the hyperosmolar state recurred either through salt retention under cortisone therapy or through water diuresis without such therapy In a separate study 100 mg cortisone/day for four days did not aggravate the diabetes insipidus and pitressin® caused no increase in renal salt loss A direct antagonism between the antidiuretic hormone and cortisone was not demonstrated in the renal tubular absorption of water or salt

Ordinarily thirst compensates for any water deficit except in the gravely ill patient or one whose sensorium is so clouded that despite large deficits of water no thirst is felt thereby accounting perhaps for hypertonicity The mechanism of thirst may be poorly integrated because a neurologic lesion interferes with perception of dehydration This is probably responsible for chronic dehydration and hypernatremia in the present case

Diabetes Insipidus in Pregnancy Salvatore C Carfagno Thomas M Durant and Charles R Shuman[5] (Philadelphia)

(5) A M A Arch I t Med. 92 542 553 Oct ber 1953

describe two cases of diabetes insipidus during pregnancy In one instance the disorder arose during pregnancy and was proved by a positive Hare test result The patient was given ergonovine but no posterior pituitary hormone during labor After delivery of a normal infant the symptoms of diabetes insipidus disappeared and results of the Hare test became negative The second patient with symptoms of diabetes in sipidus since infancy was studied during pregnancy at age 16 She had previously manifested a severe allergic reaction to posterior pituitary hormone administered by nasal insuf flation Osmotic pressure measurements performed on the plasma and urine after fluid restriction showed an abnormal response (urine/plasma osmolar ratio less than 1 0) charac teristic of diabetes insipidus After delivery of a stillborn fetus the symptoms of diabetes insipidus remained These cases are contrasted with one in which diabetes insipidus was disproved during pregnancy by normal Hare test results which thereby established the diagnosis of psychogenic poly dipsia

The exact incidence of diabetes insipidus in pregnancy cannot be accurately estimated Dystocia is by no means an invariable complication of labor in patients with diabetes in sipidus as the authors cases illustrate Perusal of the litera ture suggests that no increase in fetal mortality is to be ex pected among children born of mothers with diabetes insipi dus The Hare test is most reliable in the diagnosis of diabetes insipidus It is especially valuable during pregnancy when various psychogenic factors may operate to produce conditions mimicking true diabetes insipidus The shift of endocrine bal ance during pregnancy may be responsible for the diabetes insipidus which was present only during pregnancy in the first case reported

ABNORMALITIES OF CARBOHYDRATE METABOLISM

Effect of Purified Glucagon (Hyperglycemic Glycogeno lytic Factor HGF) on Carbohydrate and Corticoid Metab olism in Normal and Diabetic Subjects W R Kirtley S O Waife O M Helmer and F B Peck[6] (Indianapolis Ind)

(6) Diabete 2 345 349 Sept Oct 1953

point out that commercial insulin contains a substance which has a blood sugar elevating effect This substance glucagon was administered intravenously in a dose of 20 units/kg over ½ hour to normal persons and patients with diabetes of various degrees of severity and determinations of blood glucose pyruvate lactate inorganic phosphate and potassium fractional steroid excretion of urinary 17 hydroxycorticoids and 17 ketosteroids and creatinine excretion were made before and after infusion Several patients also were given the epinephrine tolerance test

Purified glucagon and epinephrine elevated blood glucose levels in all normal persons The blood inorganic phosphate level fell after administration of glucagon and epinephrine but epinephrine produced a rise in pyruvate whereas glucagon produced a fall In stable diabetics both glucagon and epinephrine produced a rise in glucose A relatively minor fall in blood inorganic phosphorus occurred after both glucagon and epinephrine were given there was no change in pyruvate level after glucagon but an elevation after epinephrine administration Stable and unstable diabetics showed *differences in their response to glucagon The stable* diabetic had a greater and more prolonged rise in blood sugar and a lesser fall in serum inorganic phosphate than the unstable diabetic The inorganic phosphate fell to levels in the unstable diabetic comparable to those of the nondiabetic

The height of the glucose response can probably be related to *the amount of liver glycogen immediately available* The unstable diabetic who may be said to have no circulating insulin presumably would have less liver glycogen than the normal person as insulin will maintain adequate liver glycogen stores Therefore the rise in blood sugar after glucagon administration would be small In contrast the stable diabetic with some circulating insulin may *have larger glycogen stores* and a greater glucagon response

During the hour of glucagon infusion there was an increase in steroid excretion as shown by the 17 hydroxycorticoid creatinine ratio

Thirty Two Cases of Renal Glycosuria James Rogers Fox[7] (Univ of Minnesota) *reports on 38 cases of nondiabetic* glycosuria found during 19 358 routine physical examinations

(7) Journal Lancet 73 275 77 July 1953

The 38 patients aged 17 37 were re examined a full history taken and a 2½ hour glucose tolerance test with 100 Gm glu cose given The follow up period was over six years in some cases

Thirty two patients (only two of them women) had normal fasting blood sugar values (below 100 mg/100 cc) with normal glucose tolerance and transient glycosuria In six cases there were normal fasting blood sugar values an abnor mally high peaked glucose tolerance curve with a return to normal level and transient glycosuria This was an incidence of so called pseudorenal glycosuria of 16 10 000 and of pos sibly latent diabetes of 3 10 000 It could not be proved that pseudorenal glycosuria had any predilection to diabetes True renal glycosuria and pseudorenal glycosuria are probably the same entity

Of the 38 patients 34 had normal weight and blood pres sures were normal in all Among the 32 with renal glycosuria 8 had a family history on one side of diabetes and 3 (all members of one family) had a history of renal type glyco suria Of the six with the high curve two had a family his tory on one side of diabetes

Three patients with nondiabetic glycosuria had been re ceiving insulin In one diabetes had been diagnosed without a blood sugar determination ever having been made He had had many insulin reactions Glucose tolerance was normal and there was glycosuria The other two patients had similar find ings It is worth repeating that one cannot make a diagnosis of diabetes on the basis of a positive sugar reaction in the urine

[The fact that three patients with renal glycosuria were given insulin shows that *their family physicians were ignorant of the proper criteria* for diagnosing diabetes mellitus This is further emphasized in the follow ing articl where 87% of the suspected diabetics referred to private physicians were studied by inadequate tests The diagnosis of diabetes cannot be discarded until a normal glucose tolerance test has been obtained, nor can it be considered established unless either a cons derably elevated fasting blood glucose value or an abnormal response to the glucose tolerance test has been found —Ed]

Diagnostic Significance of Blood Sugar Findings Chris topher J McLoughlin Lester M Petrie and Thomas E Hodgins[8] (Atlanta) report the results with a screening pro cedure for abnormal carbohydrate metabolism Each person tested was classified as having an abnormal (over 160 mg/

(8) J A M A 153 18 184 S pt 19 1953

100 cc in 2 hours or over 160 mg /100 cc at 45 minutes but below 160 at 2 hours) or a normal (below 160 mg /100 cc. both at 45 minutes and at 2 hours) blood sugar metabolism on the basis of an initial *screening test* and a *modified glucose* tolerance test Of 241 451 patients examined 4 524 (1 87%) had abnormal carbohydrate metabolism (Fig 103) Of these 415 (9%) gave a history of diabetes Of the remaining 4 109 follow up reports were obtained for 1 981 Of the 913 patients classified by the authors as borderline cases 186 (20 4%) were diagnosed by their physicians as new diabetics Ab-

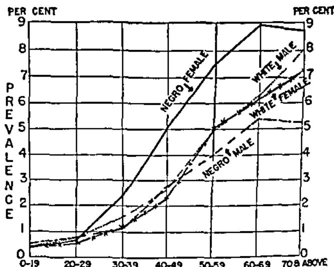


Fig 103 —I e l e f abnorm l ga met bol m n 10 ye r age g oups. (Courtesy of M Lo ghl n C J *et al* J A M A 153 182 184 Sept 19 1953)

normal tolerance curves were found by the authors in 1 068 629 (59%) were diagnosed as new diabetics There are probably many cases of diabetes among the 1 166 so called non diabetics

The laboratory procedures used by the family physicians for diagnosing diabetes were urinalyses fasting blood sugar tests postprandial blood sugar glucose tolerance including Exton Rose tests and other tests such as that for basal metabolism The Folin Wu method was used almost universally for blood sugar determination Intravenous glucose tolerance tests and insulin tolerance tests were not reported Simple urinaly

sis or a fasting blood sugar test was used to substantiate or deny the presence of diabetes in more than 76% of all cases Of the referred persons 82% were classified as nondiabetic by physicians on the basis of no laboratory work at all or only urinalysis or fasting blood sugar test

Some of these referred patients had more than 400 mg / 100 cc blood sugar on screening or glucose tolerance tests There were 443 with diagnosis of no disease although only 6 glucose tolerance tests and 162 fasting blood sugar determinations were done in this entire group the remaining 275 had diabetes ruled out by urinalysis and clinical judgment The diagnosis of no disease was made for the 162 given fasting blood sugar tests despite the fact that in 42 cases the fasting blood sugar value was over 170 mg /100 cc Most of the referred patients had a nondiabetic diagnosis by their physicians on the basis of a series of tests which from every standpoint were inadequate to rule out this condition

Prediabetic Syndrome Large Babies and the (Pre)diabetic Father Data collected by W P U Jackson[9] in the Cape Town area of South Africa indicated that women who have overt diabetes later in life are apt to have large and stillborn babies Over 60% of such women studied said they had babies weighing more than 10 lb at birth There is little evidence for and much against the hypothesis that the babies are large because of an excess of circulating growth hormone Acromegalics do not appear to have a tendency to produce babies of excessive size

The birth weights of two series of children of prediabetic and diabetic fathers one from Cape Town and one from Boston were compared with those of children of control fathers to determine whether the high birth weight might be an inherited characteristic linked in some way with the diabetic genetic make up of the father Whether the father was prediabetic or diabetic at the time of conception is not important since the germ plasm is presumably the same in both Both groups are therefore considered under (pre)diabetic Not only was there a larger proportion of 10 lb babies in the (pre)diabetic father groups but there was a general tendency for their babies to be larger than those of the control fathers (table) The incidence of large babies was not so high as in the prediabetic mother groups The percentage of infants of

(9) J Cl E doc J 14 177 183 F bru ry 1954

over 10 lb of prediabetic mothers was 31% of (pre)diabetic fathers 14% and of normal parents 5%

This study suggests that the tendency to produce large babies is partly an inherited characteristic combined with a tendency to diabetes passed on by the male as well as the female and partly an effect of maternal internal environment The difference between the figures for prediabetic mothers and (pre)diabetic fathers must be due to purely maternal

DATA ON COMBINED CAPE TOWN AND BOSTON (PRE)DIABETIC FATHERS AND CONTROLS

	TOTAL NO	FATHERS WITH AT LEAST 1 CHILD OVER 9 LB	FATHERS WITH AT LEAST 1 CHILD OVER 10 LB
(Pre)diabetic fathers	117	44	20
Control fathers	151	14	8
Difference	—	30	12
S E of difference	—	9 8	4 3
Difference/Its S E	—	3 0	2 8

factors the difference between the figures for (pre)diabetic fathers and controls must be due to inherited factors Since the late fetal death rate in the (pre)diabetic father groups and in the controls is virtually the same the excessive fetal loss in the prediabetic mother group must be entirely mediated by special maternal factors The stillbirth rate for prediabetic mothers was 15% for (pre)diabetic fathers 3 3% and for normal parents 4%

Some Emotional Aspects of Diabetes Mellitus **and the Role of the Physician** are considered by Samuel Stearns[1] (Harvard Med School) Diabetes because of its long asymptomatic period its restrictions in diet and the need of positive participation by the patient presents a unique problem in treatment Many difficulties begin when the diagnosis is first mentioned to the patient Only a few approach the problem realistically To some the illness is merely a *little sugar* This attitude either stems from a similar view of friends or relatives with diabetes or arises as a defense against having *to deal consciously with the implications of* the diagnosis It is wise for the physician to proceed cautiously in breaking down this resistance Contrariwise many patients are alarmed out of all proportion to the reality of the situation

Initial reassurance should be limited to positive aspects *to*

(1) New England J Med 49 471-476 Sept. 17 1953

conveying the physician s own confidence and to giving simple honest direct answers in the least disturbing manner to the patient s questions Anxieties which arise from the patient s personality previous family experience with diabetes and life setting may be dealt with later The approach to the patient should be individualized The intelligent independent patient should be permitted to retain his role and to consider himself an active coparticipant The excessively dependent patient should have the treatment carefully explained and as much of it as possible carried out by the physician dietitian clinic or visiting nurse There is also an intermediate type of patient who requires an individual approach

Interpersonal difficulties involving patient and physician are most commonly expressed in ways that lead to the patient s being designated un co operative These behavior difficulties are reflected in unnecessarily and frequently broken appointments *repeated tardiness unreasonable demands and failure* to accept or carry out prescribed treatment

The physician must understand that the average diabetic whose diet is to be curtailed cannot be approached only on the basis of personal appearance and health but must also be treated on the basis of what is practical realistic and emotionally feasible This approach necessitates the reorientation of the physician in several ways The prescribing of one of several stock dietary formulas invites patient failure in maintaining the diet since no consideration has been given to the patient s cultural and national food habits or to his needs as an individual

The patient s co operation must be obtained not through anxiety or fear of the disease or the physician but through the wish to be well and to gain the physician s approval

[*In diabetes as in most chronic diseases treatment must be carried* out by the patient with the physician as adviser Stearns program encourages patient participation and insures co operation On the other hand attempts to control the diabetic patient by threats coercion or admonition breed rebellion and deception Both the patient and the physician should benefit from the sane suggestions outlined here —Ed]

Paradoxical Hyperglycemia in Diabetic Patients Treated with Insulin Gerald T Perkoff and Frank H Tyler (Univ of Utah) report on 10 diabetic patients with (1) deterioration of diabetic *regulation with increased insulin doses* (2) *infre*

( ) M t bol m 3 110 117 M h 1954

quent clinical hypoglycemic reactions (3) cyclic glycosuria and (4) improved diabetic regulation on reduced insulin dosage *In each patient the increase in insulin dosage over a period of a few weeks to many months was associated with* increasing hyperglycemia and glycosuria *In one patient 48 hours after reduction of insulin dose from 110 to 60 units* daily the 24 hour glucose excretion was decreased from 25 to 2 Gm daily

Attempts to demonstrate periods of subclinical hypoglycemia in these patients were inconclusive possibly because of the rapidity with which changes in blood sugar content occur However a marked drop in blood sugar immediately after meals was observed in a few patients while they were receiving excessive doses of insulin This is *in striking contrast to the normal postprandial hyperglycemia A theoretical explanation* of this is that absorption of glucose from the bowel may temporarily interrupt glycogenolysis and diminished *peripheral utilization of glucose caused by epinephrine action* In the presence of excess insulin the blood sugar level falls resulting in decreased postprandial excretion of glucose The *mechanisms for response to hypoglycemia are thereby reactivated* resulting in rapid increase in glycosuria

Elderly diabetics manifesting paradoxical hyperglycemia *can be treated by reducing insulin dosage Juvenile diabetics* require gradual reduction of insulin

Paradoxical hyperglycemia should be suspected in any *diabetic who does not improve or whose diabetic regulation* deteriorates as the insulin dose *is* increased *Proof of this* phenomenon depends solely on the result of reduction of the *insulin dose In general laboratory studies are of* little aid in diagnosis A decrease in glycosuria after meals may possibly be of diagnostic significance Measurement of *hourly* excretion *of glucose throughout the day is a simple* clinical test

[It is difficult to overestimate the importance of this frequent error of diabetic management It is particularly prone to occur when physicians attempt to prevent even traces of glycosuria.—Ed.]

Insulin Reactions Manifestations and Need for **Recognition of Long Acting Insulin Reactions** are discussed by Robert K. Maddock and Leo P Krall[3] (Norfolk Va) Sweating hunger *tremor and palpitation are commonly recognized* signs of the hypoglycemic state Prolonged or marked hypoglycemia

(3) A M A Arch I t Med 91 695 703 J e 1953

results in abnormal behavior double vision unconsciousness and other serious central nervous system symptoms which may be used as a measure of the degree of severity of insulin reaction Headache minor personality disturbances difficulty in speech and vision automatic behavior and central nervous system symptoms may occur without the obvious symptoms of hypoglycemia The central nervous system type of re action became common with use of long acting insulins The symptoms may be mild but the hypoglycemia extreme The patient s intelligence is reduced and he may fail to eat or con tinue excessive physical exertion making the hypoglycemia worse He is in serious danger in traffic

The epinephrine like reaction probably due to an excess of circulating epinephrine follows a rapid fall in blood sugar level and results from the injection of fast acting insulin or sudden and excessive physical activity The central nervous system type of reaction is due to a depression in function of the central nervous system the exact mechanism is poorly understood During sleep or relative inactivity the need of the central nervous system for glucose is greatly reduced and therefore a slowly developing hypoglycemia could remain ob scure Frequently there may be symptoms of both types of reactions at the same time with one or the other predominat ing

CASE 1 —Man 37 late each day had giddiness was irresponsible and drove carelessly On several occasions he had convulsive sei zures One day he became unconscious and was hospitalized as hav ing epileptic seizures All these symptoms began when his physi cian had him change from the 40 to the 80 unit/cc insulin and the patient not understanding the change had doubled his insulin in take

CASE 2—Man 32 had had diabetes for four years He took insulin haphazardly and rarely tested his urine for sugar He was hospitalized in coma after he omitted breakfast one morning It took a w ek for memory and orientation to return to normal Complete study revealed active moderately advanced pulmonary tuberculosis and very brittle diabetes mellitus When hypoglycemic he was sullen and negativi tic denying any reaction and refusing orange juice Because of paucity of typical symptoms these manifestations were misinterpreted He was probably already in hypoglycemic reaction when he refused breakfa t took his insulin and went to work since the protamine zinc in ulin would exert its influence only later in the day

CASE 4—Woman 37 had had diabetes for eight years The daily dose was 60 units of protamine zinc insulin She frequently

awakened mornings feeling disagreeable and argumentative Many breakfast time emotional crises took place with her husband She refused to eat and became verbally violent She had dull headaches and automatic type of behavior Adjustment of insulin dosage and diet relieved symptoms

[Since long acting insulins produce bizarre hypoglycemic symptoms the utmost vigilance is necessary to avoid falling into the errors described by Perkoff and Tyler (preceding article) —Ed]

Insulin Zinc Suspensions J D N Nabarro and J M Stowers[4] (Univ College Hosp London) describe insulin zinc suspensions as a group of long acting insulins which contain insulin precipitated with zinc and resuspended in an acetate buffer Duration of the hypoglycemic action depends chiefly on the size and form of the insulin particles Two basic suspensions are prepared One called semilente has amorphous insulin particles and a hypoglycemic action of 12 16 hours and is available in a strength of 40 units/cc The other called ultralente contains crystalline insulin has an action of 30 hours or longer and is available in a strength of 40 units/cc Clinical trials in Denmark proved that most diabetic patients can be controlled with a single daily injection of a mixture of 3 parts amorphous to 7 parts crystalline suspension called lente with action of approximately 24 hours and available in both 40 and 80 units/cc

The actions of insulin zinc suspensions were studied in 22 hospitalized diabetic patients by means of blood sugar estimations repeated over a 24 hour period Insulin zinc suspension (lente) proved unsatisfactory in 10 of 19 patients who required more than 48 units a day In most the action was too short and better control was achieved with a mixture of lente and ultralente It is therefore recommended that crystalline insulin zinc suspension (ultralente) be made available in a strength of 80 units/cc There have been no reactions to injections of insulin zinc suspensions

Patients whose diabetes is well controlled with a single daily injection of PZI or globin insulin are unlikely to benefit in any way from the new insulin zinc suspensions unless currently used insulin causes allergic reactions Indications for trial of the new insulins are poor control on present insulins current need of morning and evening injections current need of PZI and soluble insulin in the morning by separate injection and allergic reactions to other types of insulin

(4) B t M J 2 10 7 1030 No 7 1953

Contraindications to the new insulins are brittle diabetes with insulin requirements varying from day to day and the need for more than 80 units a day It will often be necessary to adjust both diet and insulin dosage on transfer to the new preparations The carbohydrate in the diet should be so distributed that most of it is taken at lunch and tea to cover the period of maximal insulin action

Studies to ascertain whether the action of insulin zinc suspensions could be shortened by mixing them with soluble insulin thereby dispensing with the need for amorphous insulin zinc suspension suggest that this might be possible if the properties of the acetate buffer in insulin zinc suspensions were altered but further study is required

Lente Insulin (Insulin Zinc Suspension) Further Studies Wilfrid Oakley (King's College Hosp) used lente (Novo) insulin to control diabetes in 29 patients 8 of them previously untreated In 11 patients with old diabetes that had been controlled with soluble insulin with or without PZI or globin insulin the same quantity of lente insulin was given in a single dose control was better in 7 good in 1 the same in 2 and worse in 1 In 10 other old cases no comparison of the degree of diabetic control obtainable by the use of lente and that of the older insulins was made control with lente was good in 5 fair in 2 poor in 2 and failed completely in 1

In eight new and untreated cases of severe diabetes lente exerted good control in six and fair and poor control in one each Of 14 outpatients treated with lente 10 were new untreated diabetics and 4 had relatively mild long standing disease control was good in 8 of the 10 new cases fair in 1 and insufficiently followed but believed well controlled in 1 of the 4 long standing cases lente controlled 3 but the fourth patient was too un co operative to be reliable

No significant local and remarkably few hypoglycemic reactions to lente insulin have been noted Patients are apparently most likely to have hypoglycemic reactions during the morning or afternoon whereas nocturnal reactions are uncommon

The New Insulins—Lente Ultralente and Semilente— were studied by Ian Murray and Robert B Wilson[6] (Glasgow) in 15 females and 13 males aged 14-72 who had been diabetic

(5) Brit M J 2 10 1 10 3 N 7 1953
(6) Ibid pp 10 3 10 6

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(4) B M J 10 1030 N 7 1953

arms and both buttocks Insulin atrophy was marked in the arms within nine months of starting the injections No subcutaneous atrophy developed in the 20 months that the insulin hyaluronidase mixture 64 68 units/day had been given in the anterior abdominal wall only

In two other cases the addition of hyaluronidase prevented atrophy whereas with insulin alone atrophy appeared after a few months in each If the value of this method is confirmed it would alleviate this side effect of insulin which occurred in 10 of 20 diabetic children under the authors care

The insulin hyaluronidase mixture is prepared daily since the spreading action begins to diminish after eight hours A more stable preparation would have obvious advantages It is probable that the dose of hyaluronidase used by the authors is excessive

Effects of General Anesthesia and Hexamethonium, on Blood Sugar in Nondiabetic and Diabetic Surgical Patients were studied by J A Griffiths[8] (Sheffield England) after two diabetic patients had severe hypoglycemia toward the end of surgery in which the technic of hexamethonium induced controlled hypotension for the reduction of blood loss was used

The anesthetic technic consisted of induction with 5% thiopental sodium and gallamine triethiodide given intravenously inflation with oxygen and orotracheal intubation Maintenance was by nitrous oxide oxygen (60 40 %) on the semiclosed circuit with carbon dioxide circle absorption supplemented by pethidine intravenously and further doses of gallamine when required Hexamethonium 40 50 mg was given intravenously after induction Respiration was assisted when necessary to insure full oxygenation at all times

In selected nondiabetic patients the following results were obtained (1) During superficial operations in 20 subjects blood sugar values remained constant throughout (2) Upper abdominal section in 10 patients produced a maintained rise of the blood sugar level which was statistically significant but clinically unimportant (3) During superficial operations in 25 cases under induced hypotension with hexamethonium bromide the blood sugar decreased after hexamethonium was given remaining stable at this lower level

In two nondiabetic patients hexamethonium greatly potentiated the action of parenteral insulin causing severe hypo

(8) Q t J Med 88 405 418 Oct b r 1953

from 2 months to 30 years In every patient formerly controlled on a mixture of soluble and protamine zinc insulins the control with lente was at least equally good and in several even better Among three patients who had previously required morning and evening injections and were now given lente the result was extremely satisfactory in one in the other two although fasting blood sugar level was normal levels early in the day were too low

The action of ultralente was more prolonged than that of protamine zinc insulin but when used alone, it failed to control hyperglycemia for several hours after injection The authors experience with semilente is limited and inconclusive but its action appears to resemble that of soluble insulin

In one patient after failure of protamine zinc to control properly a mixture of 52 units of lente and 32 units of ultra lente gave better control than ever before One patient with diabetes for 22 years best controlled with 44 units of protamine zinc and 16 units of soluble insulin had definite improvement from 28 units of semilente and 48 units of lente and remained symptom free without hypoglycemic attacks

No conclusions were drawn in five cases In four a mixture of lente and ultralente might have proved satisfactory but had not been tried In one patient fluctuations in control associated with asthmatic attacks made comparison of the different types of insulin impossible

Two patients previously well controlled deteriorated rapidly on change to lente insulin

There were no local allergic reactions to the new insulins even in patients who had previously had troublesome lumps

[The use of long acting zinc insulin crystals should obviate the sensitivity reactions sometimes produced by protamine or globin in the long acting insulin preparations now in clinical use These studies show that further investigation is needed before this potential advantage outweighs the disadvantages of abandoning established modes of treatment —Ed]

Method of Preventing Insulin Atrophy by use of a daily made mixture of 3 mg of hyaluronidase in 400 units soluble insulin (80 units/ml) is reported by J G Fox R B McConnell H S Pemberton and D C Watson[7] (Liverpool) The added hyaluronidase caused no change in diabetic control and did not increase discomfort on injection

Girl 7 diabetic for two years had severe insulin atrophy of both

(7) Brit. M J 2 1202 1203 Nov 28 1953

pression that more thorough control of diabetes yields a higher survival rate one almost equaling the rate among non diabetic tuberculous patients in the same institution receiving the same therapy for tuberculosis

There is no essential difference in the localization of the tuberculous infection in the diabetic and nondiabetic Onset is no more insidious but it is often missed which makes as pertinent as ever *the old rule that in every diabetic who is not* doing well without apparent cause suspect tuberculosis

At Montefiore Hospital no limitation is placed on the treatment plan of the tuberculous patient because he has diabetes Under proper management there is no reason to fear ketosis There were fatalities from coronary thrombosis after thoracoplasty even when all precautions were taken But generally these patients can be treated for tuberculosis as if diabetes did not exist Multiple stage thoracoplasties cavernostomies segmental resections lobectomies and pneumonectomies are performed without hesitation Chemotherapy is used according to the developing concepts Isoniazid therapy is accompanied occasionally by increased appetite and food intake The possible increase in insulin requirement is offset by the decrease in such requirement from the improved febrile state The important principle is to treat the disease vigorously Prompt hospitalization is essential There were many cases of bilateral spread due to delay from ill advised bed rest or sanatorium cures

In therapy an attempt is made to keep the urinary glucose within 10 20 Gm daily Above all hypoglycemia with its attendant dangers of unconsciousness aspiration of infected *material* and bronchogenic spread *must be avoided* A slight glycosuria will avoid this hazard

Preliminary analysis of the first 100 cases (1936-41) showed a five year mortality rate of 24 2% in diabetic tuberculous patients against a rate of 22 9% in nondiabetic patients

[Alth ugh Ga s believes close diabet c control may improve the prognosis of h s tuberculous d abetic patients Ferrara concluded that there was no relation between diabetic control and the progre s of the disease (New England J Med 246 2 1952) —Ed.]

Diabetes in Pregnancy produces a high incidence of complications In an attempt to evaluate the outcome of a diabetic pregnancy in competent obstetric hands under good medical

glycemia Three patients with controlled diabetes showed stable blood sugar values with the standard anesthetic technic Considerable potentiation of insulin occurred in one further diabetic patient in whom hypotension was induced with hexamethonium

It was noted that hexamethonium in the anesthetized subject masked many of the signs of hypoglycemia even when severe The only constant sign was progressive tachycardia The author concludes that controlled hypotension with hexamethonium is strongly contraindicated in diabetic patients because of (1) the common complication of peripheral vascular disease in such patients and (2) the danger of severe hypoglycemia with possible resultant acute coronary insufficiency or central nervous system damage

[Hexamethonium is also dangerous when used as an antihypertensive agent in diabetics Previously well controlled patients have had severe hypoglycemic reactions without appreciable reduction of the blood pressure level —Ed]

Diabetes and Tuberculosis Elmer S Gais[9] (Montefiore Hosp New York City) considers the fact that this combination of diseases is fatal unless it is recognized early and vigorous treatment is instituted For 1926 36 Wiener and Kavee reported a mortality of 79% in 218 patients within three years after onset of tuberculosis More recently Ferrara reported that only 3 of 68 patients lived longer than six years and 50% died within two years The incidence of tuberculosis is higher in diabetics than in the general population The most recent evidence is presented in the Philadelphia survey in which 8 4% of the 3 106 diabetics studied were tuberculous whereas 4 3% of 70 767 industrial workers had tuberculosis This survey also showed that tuberculosis was active in 2 6% of diabetics that the prevalence of active tuberculosis increased greatly with severity of the diabetes and that in the younger age group its prevalence was much greater in those with diabetes 10 years or more

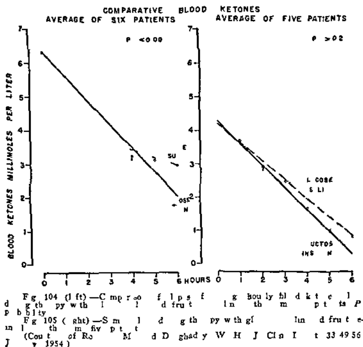
When the younger age group only was considered a history of coma seemed to have a slight positive influence on the incidence of tuberculosis If underweight is evidence of undernutrition and inadequate control then the increased incidence *in this group* may reflect the hazard of poor diabetic control

From a study as yet incomplete Gais has gained the im

(9) N w Yo k J Med 53 1844 1846 A g 15 1953

addition of carbohydrates to insulin in diabetic acidosis actually speeds recovery from ketosis An attempt was made to achieve equivalent initial ketosis in all studies of the same patient by withdrawing insulin for one to three days Average initial level of blood ketones was 5 1 mM /L

Blood ketone levels fell more rapidly after intravenous administration of glucose and fructose than after saline in



F g 104 (l ft) —C mp r so f l p s f g hou ly bl d k t e l d g th py w th l l d fru t l n th m p t ts P p b b l ty

F g 105 (ght) —S m l d g th py w th gl lin d fru t e in l th m fiv p t t

(Cou t of Ro M d D ghad y W H J Cl n I t 33 49 56 J y 1954)

insulin treated patients with diabetic ketosis (Figs 104 and 105) The rate of this fall of blood ketones was not significantly different whether glucose or fructose was used The more rapid drop in blood ketone levels after carbohydrate therapy might be explained by (*a*) increased renal loss (*b*) increased peripheral utilization or (*c*) decreased hepatic production of ketones The most likely explanation is inhibition of hepatic ketogenesis

management on insulin alone without use of hormones and the advantages to be gained from the use of hormones (hormone meaning any sex hormone natural or synthetic) Walter S Jones[1] (Providence R I) reviewed 100 962 deliveries (1927 51)

Of 184 diabetic pregnancies 158 reached viability (960 Gm) without hormone therapy and 4 with only subclinical doses of hormones Congenital anomalies were 3 times breech and other malpositions 3½ times and prematurity (living and stillborn) 4 times as common as the 1946-50 incidence among nondiabetics in the same hospital There were no maternal deaths or therapeutic abortions among the 162 diabetics Diabetics do not abort more often than normal women (10% average) The outcome of a diabetic pregnancy hinges on control of the diabetes There were 44 (26 9%) cases of acidosis with gross fetal loss of 23 (52 3%) infants There were 69 (42 6%) cases of toxemia with fetal loss of 22 (31 9%) or 14 times the over all 10 year toxemia rate reported for the same hospital Fetal loss was 21 2% among nonacidotic and 52 3% among acidotic mothers Fetal salvage is the ultimate test of any method of treatment and excessive preventable loss occurred from acidosis Better management could have improved the toxemia picture One fourth of the fetal loss was caused by prematurity anomalies and inevitable accidents Of the remainder 29 were associated with acidosis toxemia or both If just these two complications could be eliminated fetal loss would be reduced to 12 7%

Obviously hormone therapy has not reduced toxemia in diabetes White s incidence in 439 cases was 44% The incidence *among* the combined small hormone series of Palmer Randall Hurwitz and Rike comes to 43% Diabetic patients *not* given hormone therapy by Hall Hurwitz and in the author s series together total 556 pregnancies with a toxemia incidence of *37%*

Comparison of Insulin Treatment with and without Added Carbohydrate in Human Diabetic Ketosis Marvin Rosecan and William H Daughaday[2] (Washington Univ) compared forms of therapy by inducing ketosis 20 times in eight diabetic patients to settle the controversy over whether or not the

(1) Am J Ob t. & Gynec 66 3 2 334 A gu t 1953
(2) J Cl n In t, 33 49 55 J ty 1954

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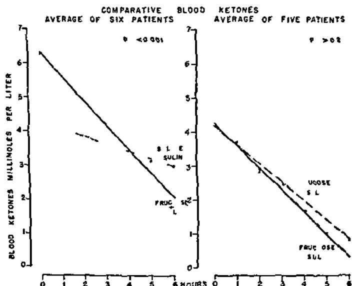


Fig 104 (left) —Comp rison f l pes f er g hou ly blood keton v l es d n ther py w th sal e-insul n and fru tose ul n th sam s p tients P p b b li y

Fig 10 (ght)—S m al d a ther py w th gl cose-in l n fructose-insul n the same 6 p tients

(Courtesy f Raseca M d Da gh day W H J Cl In est 33 49 56 Ja ary 1954)

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Average tissue uptake of carbohydrate with insulin and saline was 34 Gm with glucose and insulin 81 Gm and with fructose and insulin 127 Gm The antiketogenic effect of glucose or fructose given intravenously in the presence of insulin did not differ Despite virtually normal rate of removal of fructose from the blood of diabetics without insulin the full antiketogenic effect requires insulin Infusion of fructose without insulin *in one case resulted in a calculated tissue* uptake of only 14 Gm sugar as against 95 Gm with the use of insulin The more effective suppression of ketogenesis can be attributed to increased tissue uptake of carbohydrate *whereas decreased uptake in the absence of insulin instead* of being a failure to remove fructose from the blood is due to the conversion of fructose to glucose by the liver and perhaps the intestines and the subsequent release of glucose from liver cells into the blood

The judicious use of fructose can obviate hyperglycemia and the resultant intracellular dehydration osmotic diuresis and electrolyte loss that used to accompany early glucose therapy

Fructose in Treatment of Diabetic Ketosis was found by J H Darragh R A Womersley and W H Meroney[3] (Yale Univ) superior to glucose for correction of cellular dehydration and hypertonicity of body fluids Fructose enters the cells by phosphorylation to form fructose phosphate under the influence of fructokinase which does not require activation by insulin thus circumventing one of the blocks in carbohydrate metabolism in diabetes mellitus However fructose administered without insulin is not more antiketogenic than glucose

Because glucose does not enter the cells readily it contributes to the effective osmotic pressure of the extracellular fluid and thus promotes loss of intracellular water Hypotonic electrolyte solutions have been recommended in diabetic acidosis to correct this effect but there are objections to their rapid infusion in large volume Hence isotonic glucose 5% or mixed with isotonic saline (2 5% glucose in 0 45% saline) has been used as a vehicle even when carbohydrate metabolism is severely disturbed Glucose administered early in the course of treatment of diabetic ketosis either increases the blood gluco e or delays its return to normal .

(3) J Cl I t 3 1 14 1 1 De mbr 1953

Fructose was found to have advantages over glucose Part of the fructose is utilized whereas glucose would be excreted quantitatively in urine Fructose administered intravenously is removed more rapidly from the blood releasing the water With adequate insulin it does not produce an increase in blood glucose

Parenteral fluid therapy of diabetic ketosis was therefore begun with fructose 2 5% in 0 45 NaCl which provides an isotonic solution without increasing the effective osmotic pressure of extracellular fluid In severe diabetic acidosis with shock blood volume should be expanded with blood plasma or colloid solutions Once the blood sugar content has begun to fall and hypertonicity has been corrected 5 or 10% glucose should be used to prevent hypoglycemia

[The preceding two papers are representative of several published recently of studies on the use of fructose in treatment of diabetic acidosis It is agreed that this hexose is preferable to glucose as a vehicle for water but it does not alter the need for insulin —Ed]

Growth of Juvenile Diabetics Nils Bergqvist[4] (Malmo Gen l Hosp Sweden) followed the growth in height of 56 diabetic children with onset of disease before age 15 All were treated with insulin and most received a liberal unlimited diet without sweets The therapeutic aim was to keep the patient free from diabetic symptoms without troublesome hypoglycemic reactions acidosis or glycosuria During an observation period averaging 5 3 years general but not severe retardation of growth was noticed most pronounced in boys Periods of slow increase in height are characterized by rapid increase in weight

In addition data were collected on 11 diabetic dwarfs in all of Sweden In these a constitutional factor probably contributed to the subnormal height The majority had a diet low in calories and carbohydrates and probably because of this received relatively small insulin doses At least nine patients had hepatomegaly Delayed development of the genitals or indications of hypogonadism or both were encountered in all patients and were probably of a hypophyseal origin Four of the 11 patients were girls and all had low 17 ketosteroid values indicating deficiency of adrenocortical steroids which is possibly of a hypophyseal origin Other signs of lack of pituitary hormones were not noted

(4) Acta endocr 1 15 133 165 Febru y 1954

Observations from animal experiments give strong support to the view that insulin is an essential hormone for normal growth Lack of insulin is a major cause of growth disturbance in diabetics The greater tendency to growth disturbance in boys than in girls is possibly explained by a defective gonadal function as androgens are obviously important for growth of boys whereas estrogens do not have the same influence in girls

[Diabetic infantilism is usually associated with a greatly restricted dietary intake and consequent underinsulinization i e it is a form of starvation It seems unlikely however that undernutrition could account for the slight growth retardation of the diabetics described by Bergqvist, since they tended to be overweight —Ed]

Relation of Diabetic Hypertension to Age and Duration of Diabetes is discussed by St Greif and E Moro[5] (Graz Austria) who measured the systolic tension of 289 diabetics The correlation between age and hypertension was as expected but not so between the duration of illness and hypertension It is therefore suspected that the metabolic error is *not in itself decisive in the origin of diabetic hypertension* Among the diabetics were some with the Kimmelstiel Wilson sydrome in them renal hypertension was closely correlated with the duration of the diabetes

Diabetic retinopathy and intercapillary glomerulosclerosis are the best examples of vascular disease dependent on metabolic error Premature arteriosclerosis of coronary vessels and arteries of the legs is also correlated with the duration of diabetes The seemingly idiopathic albuminuria found only in patients with ophthalmoscopically visible capillary changes of the retina led to the concept of specific diabetic capillary damage

***Incidence of Peripheral Vascular Changes in Diabetes* Mellitis Survey of 264 Cases** is presented by Otto Brandman (Newark N J) and Walter Redisch[6] (New York City) The youngest patient was 17 the oldest 64 about 70% were aged 20-40 In most of them diabetes began in early adult life

About 30% of the patients showed some evidence of relative peripheral arterial insufficiency within five years of onset of diabetes This percentage does not increase significantly *within* the succeeding 5 years it rises above 52% within 15

(5) W n kl Web sch 65 956 958 Nov 20 1953
(6) Diabet 2 194 198 May J ne 1953

years Since it is a well known fact that the incidence of obliterating arteriosclerosis of the lower extremities increases with age the incidence of relative peripheral arterial insufficiency of the lower extremities is surprisingly high in cases with only up to five years known duration of diabetes

Hypertension was fairly common Of 64 hypertensive diabetics 23 had signs of relative peripheral vascular insufficiency The incidence of obesity was high Whereas the incidence of hypertension in the whole group was 24 3% among the obese it was 43% The incidence of peripheral vascular damage was equal among the obese and nonobese

Control of diabetes was considered good if urinary excretion of glucose did not exceed 10% of the carbohydrate intake fasting blood sugar level was not above 150 mg /100 cc (180 mg in older groups) and if there were frequent medical check up and urine examinations strict adherence to diet subjective feeling of well being maintenance of adequate weight and immediate consultation if any metabolic derangements were noted Control was considered fair if urinary glucose content was up to 25% of the carbohydrate intake fasting blood sugar level was 150 250 mg /100 cc and if there were infrequent medical check up occasional laxity in diet no weight loss and irregular urine examinations Control was poor if urinary glucose content was over 25% of carbohydrate intake fasting blood sugar level was over 250 mg /100 cc and if there were rare medical check up intermittent loss of weight lack of energy etc laxity in adherence to diet and insulin and presence of acidosis

Statistics do not indicate that the degree of control of diabetes was a factor in development of peripheral vascular disease There might be some suggestive evidence of high incidence of retinal hemorrhage in the poor group (12%) compared to the good group (3½%) The other vascular manifestations were about equally distributed among the three groups

[The preceding articles emphasize the fact that vascular disease does not develop uniformly in diabetes but affects certain vessels (kidney ocular fundus peripheral arteries) preferentially The lack of correlation between diabetic control and atherosclerosis although contrary to the findings of Wilson *et al* (Am J M Sc 221 479 1951) and Allen (New England J Med 248 133 1953) is in agreement with the observations of many other authors including Herzstein and Weinroth (Arch Int Med 76 34 1945) Dolger (J A M A 134 1289 1947) and Tolstoi (M Clin North America 34 485 1950) —Ed]

Observations from animal experiments give strong support to the view that insulin is an essential hormone for normal growth Lack of insulin is a major cause of growth disturbance in diabetics The greater tendency to growth disturbance in boys than in girls is possibly explained by a defective gonadal function as androgens are obviously important for growth of boys whereas estrogens do not have the same influence in girls

[Diabetic infantilism is usually associated with a greatly restricted dietary intake and consequent underinsulinization i e it is a form of starvation It seems unlikely however that undernutrition could account for the slight growth retardation of the diabetics described by Bergqvist, since they tended to be overweight —Ed]

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(5) Wien kl Wchnschr 65 956-958 Nov 20 1953
(6) Diabetes 2 194 198 May Jun 1953

Surgical Aspects of Spontaneous Hypoglycemia Due to Occult Insulinoma are discussed by F A de Peyster and R K Gilchrist[8] (Presbyterian Hosp Chicago) Surgical excision of islet cell adenomas is the treatment of choice because 5 10% are malignant and irreversible damage to the central nervous system may result from hypoglycemia Some patients may be managed temporarily on corticotropin and cortisone but this therapy should be reserved for preoperative medical management for patients refusing surgery and for those in whom the operative risk is too great for survival However some patients are refractory to even 450 mg corticotropin a day

Each of three patients with occult pancreatic insulinoma presented Whipple s triad i e (1) signs and symptoms of insulin shock usually progressive induced by fasting or exercise (2) repeated fasting blood sugar concentrations below 50 mg /100 cc and (3) symptomatic relief from dextrose administration In each instance the tumor was detected by the pathologist on serial frozen section microscopy In each patient elevated blood sugar level with an accompanying glycosuria was observed within 1½ 4 hours following subtotal pancreatectomy The hyperglycemic rebound phenomenon was previously reported by McMillan who observed blood sugar rise from 131 mg to 258 mg /100 cc within 30 minutes after excision of a solitary insulin secreting adenoma

In patients with Whipple s triad in whom no tumor is found at operation a subtotal pancreatectomy (at least to the right of the superior mesenteric vessels) should be performed This procedure should yield a 75% chance of cure for occult adenomas and according to David a 50% chance of cure for hypoglycemia due to pancreatic hyperplasia and should benefit two thirds of the patients with hypoglycemia whose resected pancreas is normal

Adequacy of surgical therapy should be substantiated during operation by (1) the demonstration of an islet cell adenoma in the surgical specimen confirmed by rapid histologic examination and (2) by a rise in blood sugar level following resection over the base level obtained from blood drawn during the exploration and before resection of the tumor A comparative hyperglycemia response in the presence of a demonstrated islet cell tumor in the surgical specimen suggests adequate resection However total resection should be per

(8) A M A A h S g 67 330 340 S ptembe 1953

Diabetic Myelopathy Hugh Garland and Deryck Taverner[7] (Leeds) point out that Bruns in 1890 described three patients aged 58 59 and 70 with diabetes mellitus of short duration who had severe pain in the hip and thigh followed by weakness and wasting of leg muscles without objective sensory loss who recovered fairly soon after dietary restriction Five patients aged 56-73 seen by the authors had the same syndrome All had had diabetes from six months to three years None had very high blood sugar levels or was ever in coma None had been treated with insulin before onset of the neuropathy When first seen neuropathy had been present for 1 15 months All complained of leg pains usually severe always asymmetrical and sometimes unilateral The pain tended to be maximal in the hip and thigh All had some wasting of leg muscles and loss of tendon reflexes in the legs again patchy and asymmetrical At some stage three had unequivocal extensor plantar responses in a fourth they were doubtful None had any objective sensory disturbance tenderness or perforating ulcers Despite age each had normal vibration sense at the ankles and all had normal blood pressure In four the protein level of the cerebrospinal fluid was high

Suitable diet insulin and active physical therapy were prescribed After initial deterioration one patient responded well after several months Three improved rapidly on institution of treatment and the oldest and least co operative showed no change in four months

One patient had previously had a similar attack with spontaneous recovery The only important difference between these five patients and those of Bruns was that the latter recovered on dietary restriction alone although this was more drastic than that practiced today It seems possible that the natural history of this syndrome is one of spontaneous improvement regardless of the treatment

Histologic studies were not possible in this series but the clinical features suggest the presence of lesions in the spinal cords Not only is the disturbance limited to motor function but the distribution of affected muscles is not compatible with the known distribution of peripheral nerves or nerve roots The extensor plantar response in three patients is unequivocal evidence of a central lesion

[This syndrome differs in symptomatology and prognosis from ordinary diabetic neuropathy —Ed]

(7) B t M J 1 1405 1408 J n 7 1953

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[8] A. M. A. Arch. Surg. 67: 330-340, September 1953

formed if no significant rise in blood sugar level is observed

[Serial blood glucose determinations during surgery might increase the chance of adequate resection in a single operation Recently developed rapid methods such as the anthrone technic (Durham *et al* Pub Health Rep 65 670 1950) would permit this type of observation without unduly delaying the operation —Ed]

Microscopic Recognition of Active Islet Cell Tumors of Pancreas in Man by means of special stains that demonstrate the beta granules is reported by S T Nerenberg[9] (Univ of Minnesota) The severity of the clinical course in six cases of active islet cell tumor was correlated with the microscopic appearance with use of a modified Gomori chrome hematoxy lin stain

It had been impossible to differentiate by microscope the actively secreting from the inactive islet cell tumors of the pancreas Hyalinization is found in both types In this series of six active islet cell tumors five cases had pronounced de granulation of beta cells in the normal part of the pancreas In all cases of inactive islet cell tumor granulation of beta cells in the normal part of the pancreas was normal

Degranulation was produced in the rat by administration of 4 units of protamine zinc insulin/75 Gm body weight de granulation is usually complete in two weeks and often fails to develop on smaller dosage The occasional failure to de granulate within the usual period with full insulin dosage cannot definitely be explained but seems somehow to be re lated to the amount of carbohydrate ingested

In the single patient with active islet cell tumor but normal beta cell granulation in the normal part of the pancreas the process resembled that in the rat getting insulin exogenously she had had symptoms for only two weeks

The rat getting exogenous insulin had hydropic beta cell changes seen in man and in animals only when there is dia betes mellitus Gomori had attributed the hydropic beta cell changes in one case of hyperinsulinism to the large amounts of glucose given preoperatively but the explanation now would appear to be that the beta cells were degranulated by the hyperinsulinism

The hyperglycemia so common after the removal of an active islet cell tumor may be described as temporary dia betes resulting from lack of insulin storage (beta granules)

(9) Am J Clin Path 24 27 34 Jan y 1954

Regranulation of beta cells is rapid depending on the amount of carbohydrate ingested In the rat this type of diabetes disappears with the return of the beta granules The mechanism of temporary carbohydrate intolerance in patients after the removal of islet cell adenoma is probably similar to that in the degranulated rat

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CALCIUM PHOSPHORUS AND THE PARATHYROID GLANDS

Primary Hyperparathyroidism Five Cases in One Family, of which three are summarized here are described by Richard N Frohner and John C Wolgamot[1] (Great Falls Mont)

CASE 3—Man 29 was hospitalized for primary hyperparathyroidism Significant was the tenderness on percussion over the left kidney Urine studies disclosed albumin 1 + and 100 white blood cells/high power field Levels of serum calcium ranged from 13 3 to 13 6 mg and of serum phosphorus from 1 3 to 2 2 mg /100 cc Serum alkaline phosphatase value was 1 2 Bodansky units X rays disclosed normal skull and extremities A kidney stone at one operation and at another parathyroid adenomas from the left anterior and from the right inferior poles were removed Three days post operatively levels of calcium and of phosphorus were 9 5 and 5 1 mg /100 cc Three weeks later these values were 10 4 and 3 3 mg

CASE 4—Woman 30 on hospitalization had a thyroid gland nearly double normal size with a 1 cm nodule in the left upper pole Blood and urine values were normal Serum calcium levels ranged from 16 8 to 18 1 mg and values of serum phosphorus from 2 1 to 2 0 mg /100 cc Serum alkaline phosphatase value was 4 8 Bodansky units X ray studies *disclosed demineralization minimal in the skull* moderate in the mandible absence of lamina dura and bilateral nephrocalcinosis Parathyroid adenomas on the left and right superior poles were removed Tetany that supervened postoperatively was controlled with calcium orally and intravenously On hospital discharge serum levels of calcium and phosphorus were 10 5 and 3 7 mg /100 cc and of alkaline phosphatase 5 6 Bodansky units

CASE 5—Woman 26 with a 2 cm nodule in the left lobe of the thyroid gland had normal blood and urine values Level of serum calcium and of serum phosphorus were 15 8 and 2 1 mg /100 cc and of serum alkaline phosphatase 0 2 Bodansky units X rays disclosed no abnormalities Two adenomas were removed on operation Latent tetany was controlled w th calcium intravenously and orally

(1) A I t M d 40 765 773 Ap 1 1954

On hospital discharge calcium and phosphorus levels were 9 5 and 1 9 mg /100 cc

Although rickets pregnancy calcium deficiency and renal insufficiency were not primary factors in any of the patients excess ingestion of phosphate could not be ruled out The families of all patients with primary hyperparathyroidism should be screened because of possible environmental factors (such as drinking water)

Hyperparathyroidism with Normal Serum Calcium H Gordon Mather[2] (King s College Hosp London) report a case

Woman 33 had pains in the legs and back for five months X rays revealed generalized osteoporosis with a moth eaten appearance of the skull Four serum calcium determinations during three months were 10 8 10 32 9 8 and 9 7 mg /100 ml Two of three plasma phosphorus estimations were below normal limits 1 7 2 2 and 1 8 mg /100 ml Serum alkaline phosphatase levels were 92 4 94 4 and 98 King Armstrong units/100 ml Blood urea and urea clearance as well as total proteins were normal An eight day calcium balance showed that on an intake of 97 mg daily average urinary excretion was 322 mg and fecal excretion 162 mg a daily negative balance of 387 mg The combination of low plasma phosphorus and negative calcium balance even in the presence of normal serum calcium made the diagnosis of hyperparathyroidism almost certain

At surgery a small parathyroid adenoma was removed from the right lower pole of the thyroid Bone pain and weakness disappeared Latent tetany was detected five days after operation by a positive Chvostek sign and the serum calcium level was 7 9 mg /100 ml On calcium lactate therapy the sign disappeared Daily urinary excretion of calcium had fallen to 40 mg 16 days after operation despite an intake of more than 3 900 mg Six months after operation the patient was asymptomatic the x ray appearance of the bones was almost normal and the phosphatase level had fallen to 14 7 units/100 ml The phosphorus level was 3 mg /100 ml and the calcium level was still normal

The normal serum calcium level was thought to be due to the effective excretion of calcium by the kidneys The short duration of symptoms and the presence of normal kidneys allowed the excess calcium mobilized from the bones to be excreted without accumulation in the blood

[Occasional normal serum calcium values in hyperparathyroidism are not uncommon Persistently normal levels are rare The value of serum phosphate determination and of urinary excretion studies is emphasized by this case —Ed]

(2) B M J 2 424-425 Aug 1953

Carcinoma of Parathyroid Gland with all the accepted criteria of malignant growth is described by Stanley Wray[3] (*Middlesbrough England*)

Man 58 had complained of aching pain in the right leg and listlessness for a few months and of thirst and increasing constipation and polyuria for two years Physical wasting blood pressure of 180/100 and normal abdominal and thoracic viscera were noted He had a palpable 15 mm nodule left of the upper pole of the thyroid gland X rays disclosed rarefaction of bones and fibrocystic disease of the right femur and a mottled skull with small multiple cysts Blood studies disclosed 20 mg calcium/100 ml serum 31 King Armstrong units of plasma alkaline phosphatase 5 King Armstrong units of plasma acid phosphatase 2 King Armstrong units of formol stable fraction and 7 Gm total serum protein 4 3 Gm albumin 2 7 mg globulin and 2 8 mg inorganic phosphorus/100 ml serum Hemoglobin content was 94% The blood was cytologically normal Sedimentation rate (Wintrobe) was 33 mm /hour The urine contained a trace of albumin the 24 hour specimen totaled 3 L and total calcium excretion (as Ca) was 720 mg Blood urea nitrogen content was 28 mg /100 ml and urea clearance 23%

A parathyroid tumor weighing 23 5 Gm was removed Histologic study disclosed an occasional mitotic figure and signs of invasion of the capsule by growing parathyroid tissue A parathyroid adenoma was diagnosed He improved postoperatively Serum calcium level fell to 7 3 mg /100 ml and finally ranged between 9 and 9 5 mg He had no tetanic symptoms Blood urea nitrogen content fell to 20 mg /100 ml and urea clearance rose to 88% X rays disclosed bone rarefaction with osteitis fibrosa in the femur and skull Calcium gluconate and vitamin D were given After about two years of health the symptoms recurred Another nodule had appeared on the left side of the neck and could be moved only with difficulty Some wasting and reduced muscular power in the legs were noted Levels of serum calcium and blood urea were 15 4 mg and 44 mg /100 ml Sedimentation rate (Wintrobe) was 20 mm /hour

Operation disclosed growth that was inoperable because all adjacent parts of the thyroid the deeper tissues of the neck the esophagus and the large vessels on the left side were involved Superficial portions of the tumor were removed and contained cells histologically identical to the earlier ones Definite evidence of invasion into adjacent muscle was found The patient died the day after operation

[This is a rare cause of hyperparathyroidism but it occurs often enough that the surgeon should attempt to remove parathyroid adenomas completely —Ed]

Dermatologic Changes in Hypocalcemia, according to John A Simpson[4] (Univ of Glasgow) include (1) abnormal

(3) J P th & B ct 66 231 234 J ly 1953
(4) B t J D m t 66 1 15 J y 1954

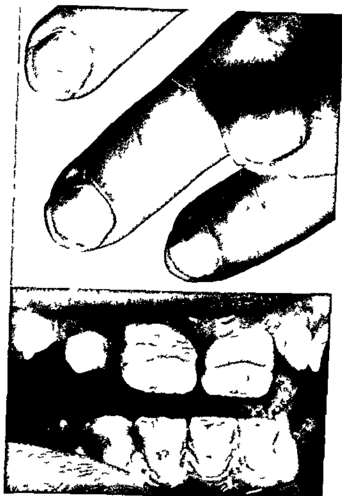


Fig 106 (top)—Id p th hypopa thy o d sm le ko ych d o y horrh t w th l g tud l pl tt g
Fig 107 (b tt m)—F owing f t th
(Co rt y of S mp J A B tt J De m t. 66 1 15 Ja u ry 1954)

growth of hair and nails with latent or manifest tetany (2) skin nail and hair changes with prolonged hypocalcemia and (3) secondary infection of skin and nails Acute hypocalcemia temporarily disturbs growth of ectodermal tissue causing shedding of hair abnormal growth of nails and possibly furrowing of developing dental enamel These changes are

more likely to appear when tetany occurs although actual carpopedal spasm is not necessary

In boy 9 with epileptic seizures and occasional spasms of tetany the skin was dry and scaly the finger nails brittle and cracked longitudinally with transverse white patches (Fig 106) the hair normal dental development greatly delayed and the enamel of incisor teeth transversely ridged (Fig 107) Serum calcium and serum inorganic phosphate levels were 5 0 mg and 6 4 mg /100 ml Treatment with calcium lactate and calciferol restored the blood picture to normal and dispelled the epilepsy and tetany Transverse grooving was not noted nor was fungus isolated from nail scrapings

Increased vascular spasm in tetany is known but the author presents the first documented instance in which angiospasm of the nail fold with subsequent grooving of the underlying nail was observed the microscopic appearance compared exactly with that in Raynaud s disease and angiospasm with tissue ischemia may explain the shedding of hair

The edema in hypoparathyroidal children is attributed to increased permeability of blood vessels with angiospasm The cause of the other changes is less certain Primary or secondary nutritional deficiencies due to malabsorption especially in patients with steatorrhea may account for some of the observed changes but pure calcium deficiency in hypoparathyroidism with chronic hypocalcemia causes dryness puffiness scaliness and pigmentation of skin brittleness and longitudinal striation of nails and scantiness of scalp eyebrow and axillary hair

The pathogenesis of impetigo herpetiformis of Hebra and mycotic infection of the nails may be traceable to defective skin or nail cells deprived of the effect of calcium for maintenance of their integrity

Neonatal Tetany in Two Siblings Effect of Maternal Hyperparathyroidism R Lee Walton[5] (State Univ of New York Syracuse) reports on two female siblings born after 8 and 8½ months gestation who had convulsions beginning on the 8th and 5th day of life and continuing until the 21st and 31st day respectively Treatment included calcium chloride and lactate aluminum hydroxide gel and calcium gluconate Serum inorganic phosphorus value was elevated to 8 and 10 mg /100 ml and serum calcium between 6 and 10 mg Both infants recovered and were discharged in good health Examination of

(5) Ped 1 13 2 7 234 M b 1954

the mother revealed primary hyperparathyroidism due to adenoma

Woman 27 had weakness anorexia loss of weight fatigue and malaise for five to six years accompanied by occasional polyuria some difficulty in swallowing headaches and vague bone pain In addition to the two premature live infants she had had one stillborn infant and two premature live infants that died She was under developed and undernourished but no specific abnormalities of any system were found There were no palpable nodules in the region of the thyroid There was slight bone tenderness in the left parieto occipital region of the skull X rays showed a punched-out area in this region resorption of alveolar bone loss of the lamina dura around the teeth and bilateral nephrocalcinosis Total serum content was 13 1 14 5 mg /100 cc ionized serum calcium 6 5 8 1 mg serum inorganic phosphorus 2 0 2 9 mg and alkaline phosphatase 13 87 Bodansky units Nonprotein nitrogen serum CO serum pH and serum chloride were all within normal limits Neck exploration revealed a parathyroid adenoma at the inferior pole of the left lobe of the thyroid gland Postoperatively total serum calcium level was 8 9 11 8 m /100 ml ionized serum calcium 4 8 6 5 mg erum inorganic phosphorus 2 1 3 6 mg and alkaline phosphatase 36 59 Bodansky units

The mechanism of intrauterine suppression of fetal para thyroid glands is incompletely understood The number of stillbirths and premature births in this patient as well as in those reported in the literature may be related to the underly ing primary hyperparathyroidism The occurrence of tetany in premature Negro or breast fed infants or in a severe form in any infant should lead to the suspicion of hyperparathy roidism in the mother

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(6) J Cl n E doc n l 13 519 533 M y 1953

thormone elicited the characteri tic respon e but dihydrotachysterol failed to lower the erum pho phoru or to elevate the erum calcium ignificantly above control level She had been maintained on a dairy product free diet calcium amphojel[8] and 1 00 000 unit of vitamin D daily but continued to manifest latent tetany with occa sional carpopedal pasms associated with erum calcium averaging 8 mg /100 cc. and pho phorus 5 mg

Two pregnancies occurred during the period of ob ervation The

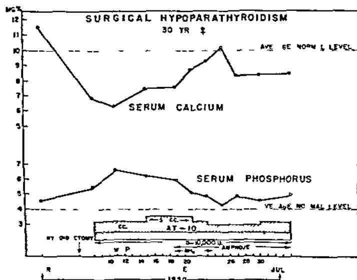


Fig 108 —Serum calci m and phosphorus level demonstrating initial f vorabl response to anti eta ic therapy d ring first hosp talization (Courtesy f Bl hm, R W J et al J Clin. Endocrinol. 13 519-533 M y 1953)

fi t was terminated by mi carriage at four months the econd went to term. She was omewhat improved during both pregnancies especially during the one that went to term but there was exacerba tion of the tetanic ymptom after delivery The living infant seemed normal at birth and after 2½ months had no signs of hyperpara thyroidism. The mother had no trophic changes.

Failure to respond to activated sterol therapy might be due to (1) failure to ingest the agents (2) failure of absorption (3) inactivation of the agents by some antigen antibody mechanism (4) excessive demand (5) physiologic antago ni m and (6) pre-existing econdary renal hyperparathyroid i m No adequate explanation was found

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(6) J Clin E docr I 13 519 533 May 1953

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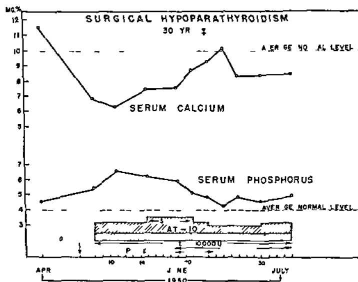


Fig 108 —Serum calcium and phosphorus levels demonstrating ... (Courtesy ... 13 519 533 May 1953)

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(6) J Cl Endocr 1 13 519 533 M y 1953

abnormality in Boeck's sarcoid which is seldom emphasized

Man 28 was hospitalized for sarcoid proved by biopsy of skin and muscle Blood values were 97 mg sugar 3 7 Gm serum albumin and 2 5 Gm globulin and 11 mg blood urea nitrogen per 100 cc The urine contained albumin and sediment contained 1 red and 4 white cells/high power field The phenolsulfonphthalein test showed 7% excretion of the dye in the first 15 minutes and a total of 28% in 2 hours A Fishberg concentration test showed the highest specific gravity to be 1 014 Serum calcium level was 14 4 mg and serum inorganic phosphorus 3 4 mg The Sulkowitch test showed 4 + calcium in the urine Calcium levels continued to be elevated with normal serum phosphorus levels Urinary excretion of calcium was 460 mg /24 hours on a diet containing 137 mg Cortisone—300 mg the 1st day 200 mg the 2d and 100 mg for the next 12 days—reduced the serum calcium level to normal by the 3d day where it remained for the six months of follow up

Renal insufficiency proved by poor tubular secretion of PSP and lack of ability to concentrate was the most important functional impairment Blood urea nitrogen level was normal Sarcoid involvement of the kidney is rare and functional impairment has not been described The elevated serum calcium level in this case suggests nephrocalcinosis as the likely renal cause of impaired function

In the literature 20-45% of patients with sarcoid had hypercalcemia The mechanism is obscure There is no correlation between the level of serum calcium and either bone lesions or serum proteins Characteristically the serum inorganic phosphorus content remains normal excluding hyperparathyroidism Persistent hypercalcemia may result in precipitation of calcium in the body tissues particularly in the urinary tract in the form of renal calculi or calcinosis of the collecting tubules

If the serum calcium values can be decreased to normal early in the process nephrocalcinosis is reversible If however the process continues uninterrupted renal insufficiency uremia and death may result

Patients with sarcoid need serum calcium determinations for persistent unrecognized hypercalcemia may lead to renal insufficiency Whether or not cortisone will consistently correct the metabolic defect remains to be proved

[The ability of cortisone to increase calcium excretion may be useful in sarcoid, but it is undesirable in patients already tending to be hypocalcemic. Patients with unrecognized hypoparathyroidism who are given cortisone for relief of myalgia may develop clinical tetany —Ed]

[Hypoparathyroidism following thyroidectomy is often difficult to control The patient s ability to carry through a normal pregnancy despite continuing hypocalcemia is the opposite of the picture presented in the hyperparathyroid mother whose babies may have tetany (see preceding article) Presumably the hyperactive fetal parathyroids of babies of hypoparathyroid mothers can return rapidly to a normal level of activity whereas the undeveloped fetal parathyroids of the children of hyperparathyroid mothers require time to develop normal secretory ability—Ed]

Cortisone Interference with Calcium Therapy in Hypoparathyroidism is dscussed by Robert C Moehlig and Albert L Steinbach[7] (Harper Hosp Detroit)

Woman 51 three days after subtotal thyroidectomy had tetany of the fingers and toes and paresthesia of the extremities and Chvostek s and Trousseau s signs appeared Serum calcium level was 7 62 mg /100 cc (normal 9 0 11 5 mg) and serum phosphorus 6 2 mg (normal 3 0-4 5 mg) Control was effected with 300 units (3 cc of parathyroid extract intramuscularly daily for two days and 2 capsules (0 625 mg each) of A T 10 daily Calcium intravenously and orally was also given She was discharged within five weeks of *hospitalization but was readmitted six weeks later because of low* serum calcium levels mental confusion and cramps in the hands *and feet She again recovered on treatment with calcium* intravenously and orally parathyroid extract intramuscularly and A T 10 She again left the hospital instructed to take calcium and A T 10 and to adjust A T 10 dosage by the results of the Sulkowitch test

She did well for 3 2/3 years when cortisone therapy was given for arthritis After a week of 25 mg cortisone twice daily the signs and symptoms of tetany grew worse Despite active antitetanus therapy the spasms in hands and feet became more severe On rehospitalization values for serum calcium were 8 3 mg inorganic serum phosphorus 6 1 mg alkaline phosphatase 3 2 mg (normal to 13 units) and serum potassium 3 9 mEq /L (normal 3 5 5 0) The Q T interval was 0 46 seconds Throughout cortisone therapy the Chvostek and Trousseau signs mental dulness and depression persisted The possibility that cortisone was interfering with control led to its discontinuance Improvement followed within three days with serum calcium level risen to 10 1 mg A maintenance regimen of 2 capsules A T 10 and 12 Gm calcium gluconate daily proved successful

Cortisone may exert its effect by decreasing calcium absorption increasing calcium excretion and lowering the total serum calcium secondary to decreased serum protein level resulting in lowering of the protein bound calcium values

Hypercalcemia of Sarcoid Corrected with Cortisone Roswell W Phillips[8] (V A Hosp Providence R I) reports an

(7) J A.M A. 154 42 44 J n 2 1954
(8) N w Engl d J M d *248 934 936 M y 28 1953*

ficiency disease such as sprue it is necessary to administer large amounts of calcium as well as vitamin D over a long time to permit bone healing These patients however can be treated adequately and still retain their parathyroids —Ed.]

Study of Mechanism of Bone Disease in Hypophosphatemic Glycosuric Osteomalacia is presented by Laurence H Kyle William H Meroney and Monroe E Freeman[1] (Georgetown Univ)

Man 52 with Fanconi s syndrome had x ray evidence of pseudo fractures and osteomalacia Serum calcium level was 10 mg phosphorus 1 8 mg and alkaline phosphatase 16 Bodansky units Urine study showed 0 16 Gm glucose daily hyperphosphaturia and a phosphate clearance of 28 cc /minute/1 73 sq m Organic aciduria was 1 8 mEq /kg /day amino aciduria 400 900 mg /day pH 6 1 ammonia 40 μEq /minute and titratable acid 21 μEq /minute acetone was present and volume was 3 000 cc /day Blood cations and anions were within normal limits

He had a high phosphate excretion despite low phosphate intake On a diet containing constant calcium and phosphorus for eight days he was in negative calcium and phosphorus balance Blood mineral values were characteristic of osteomalacia Eight days of alkali therapy did not change calcium and phosphoru balance or blood mineral values The addition of vitamin D for eight days resulted in positive calcium balance but phosphorus excretion increased During six days of increased phosphate intake a positive phosphate balance occurred and the calcium balance became nearly positive During this period serum phosphorus level rose from 1 9 to 2 5 mg /100 cc

Possible mechanisms for the osteomalacia in the Fanconi syndrome are (1) loss of metabolites necessary for normal nutritional balance (2) excessive primary urinary loss of calcium (3) disorder of organic acid metabolism and (4) excessive phosphate excretion Variation in the ingested amounts of the major components of an isocaloric diet resulted in no major change in urinary excretion of glucose amino acid or phosphate No mechanism attributable to acidosis or impaired ammonia synthesis could be found to suggest primary hypercalcinuria as a cause of the osteomalacia No excess of blood organic acid was demonstrable and quantitative comparison of blood cations and anions revealed no discrepancy attributable to an excess of undetermined anion Thus the first three mechanisms were not valid The fourth mechanism excessive phosphate excretion is the dominant mineral defect in the Fanconi syndrome

(1) J Cl E doc l 14 365 3 7 Ap l 1954

Osteomalacia in Sprue, should be common according to Harald A Salvesen and Jens Boe[9] (Rikshosp Oslo) since in sprue the fat soluble vitamins and calcium (as calcium soaps) are carried out with the feces Among 85 patients with sprue 31 had normal or slightly lowered serum calcium levels corresponding to the hypoproteinemia and normal serum phosphorus levels of the other 54 14 with somewhat but not severely lowered serum calcium and phosphorus levels were not regarded as osteomalacic whereas in 40, the chemical conditions necessary for the production of osteomalacia were present in the body fluid Of the last group only 22 had x ray signs of bone disease including Milkman syndrome and late rickets (7) tetany and osteoporosis (3) and low calcium level without tetany but with osteoporosis (12) the other 18 had characteristic osteomalacic serum but no manifest bone disease of them 7 had tetany and extremely low calcium levels and 5 had low calcium level without manifest bone disease

All patients with x ray evidence of bone disease had greater or lesser hypophosphatemia whereas serum calcium values varied In patients with Milkman syndrome and late rickets serum calcium levels might be near normal and were usually higher than in patients with osteoporosis alone in the second group three had tetany and low calcium and phosphorus levels Increased phosphatase activity characterized both Milkman syndrome and late rickets

In the 12 patients with no bone disease despite chemical conditions favorable to osteomalacia all phosphorus values were normal and on the whole calcium values were low 7 also had tetany

Actual bone disease develops when chemical conditions favor osteomalacia and when secondary hyperparathyroidism is also present Osteomalacia develops if the parathyroids are stimulated by low serum calcium levels The parathyroid insufficiency that occurs in patients who have no bone changes evidently serves to protect them from bone destruction Parathyroidectomy might be the therapeutic answer in difficult cases of osteomalacia especially if they are also of the vitamin D resistant type

[It would be more sensible to treat the hypocalcemia medically and thus reduce parathyroid hyperactivity than to suggest parathyroidectomy with its attendant problems When osteomalacia occurs in a chronic de

(9) Acta med sca d v 146 290 99 1953

presence of small amounts of fat or intestinal gas probably makes this figure too low The average water content of the LBM estimated by antipyrine dilution for 81 normal males has been reported as 71 8 ± 2 9% (range 66 3 79%) Deuterium dilution values were 69% (range 64 8 73 8%) for 12 males and 69 3% (range 66 9 74 2%) for 5 females

The concept of the fat free body is based on an extrapolation of values obtained from in vitro analyses of the percentages of several components in the residual tissues following ether extraction of carcasses to in vivo determinations of whole body composition Various authors have divided the fat free body into functional units (1) the cell mass with its intracellular water 67% (2) extracellular water 26% and (3) minerals 7%

In the military services the problem of evaluating personnel in terms of physical qualifications and capacity to perform particular tasks resolves itself into a question of dissection of an individual into performing tissues and excess fat It is suggested that the LBM/inch of height would be a more accurate description of an individual than the simple expression of per cent of excess fat and would serve to differentiate two individuals of the same height and weight one of whom is round and soft and the other rugged and muscular The mean LBM/inch of height for 25 professional football players has been reported as 2 49 (range 2 3 2 83) and for naval personnel as 1 99 The mean excess fat for the football players was 10% and for naval personnel of about the same age 16 5% If 15% above the average weight values in the standard height weight tables is considered disqualifying then 17 of the 25 football men could be rejected for military service Of the 17 11 had high corporeal specific gravity These men were overweight by usual standards but were not obese The ratio of LBM in grams to height in centimeters squared is fairly constant 2 with a standard deviation of 11%

By taking 2 lb as the average weight of the LBM/inch of height it may be estimated that the average excess fat for the 20 24 year age group is 14 lb (9% of the body weight) and for the 55 59 year group 33 lb (19% of the body weight) Overweight may be associated with either or both excess fat and lean body mass In obesity it is essential to qualify the amount of excess fat and the weight of the lean body mass

Possible causes of increased phosphorus excretion are (1) acidosis (2) competitive interference with reabsorption (3) hyperparathyroidism secondary to hypocalcemia and (4) a specific disturbance of renal tubular reabsorption The first three were not valid in this case because acidosis was not present the amount of urinary phosphate was not quantitatively related to urinary levels of either glucose or amino acid nor was it affected by changes in the basic components of an isocaloric diet The patient had a normal response to the Ellsworth Howard test in which intravenous administration of 2 cc parathyroid extract resulted in an increase of phosphate clearance from 27 to 47 cc /minute The most probable cause of the hyperphosphaturia is a specific primary defect in tubular reabsorption of that mineral The lesion may be in the proximal tubule but only limited histologic evidence is available

Lack of response to vitamin D therapy in patients with the Fanconi syndrome may be attributed to the fact that although this vitamin causes increased calcium retention it also increases the urinary excretion of phosphate

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BODY COMPOSITION AND NUTRITION

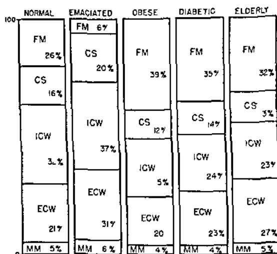
Lean Body Mass Its Clinical Significance and Estimation from Excess Fat and Total Body Water Determinations Recently developed technics for in vivo analysis of body composition have allowed many investigations important to general physiology and medical practice Albert R Behnke Elliott F Osserman and Walter C Welham[7] review these procedures and indicate certain direct applications

In vitro analyses of the fat free body have supplied data regarding protein and mineral content of the body In vivo technics by determining the specific gravity of the body as a whole and total body water by antipyrine and deuterium dilution studies have shown the presence of a basic mass of lean tissue the lean body mass (LBM) on which varying amounts of fat may be superimposed The density of the LBM is of the order of 1 100 Specific gravity of the LBM for the leanest person has never exceeded 1 100 but the inescapable

( ) A M A A ch Int M d 91 585 601 M y 1953

for any group Although the cell masses were high relative to body weight it was impossible to state whether there has been any change in the absolute cell mass The five diabetics were elderly and slightly obese as a group The average value for their total body water content was 47 7% and the average fat mass constituted 34 9%

Figure 111 shows the findings in two patients before and after treatment with testosterone One patient had carcinoma



F g 110 —V t g p t g mp t f tot l body w ght f d d l w th d ff t n t t l d p th l g tat (C t y f H mw G J d U b h S M b l n 391 403 pt mb 1953)

of the breast with metastases to the lungs and brain and the other had inactive acromegaly The carcinoma proved remarkably sensitive to testosterone therapy and after two months treatment the lethargic moribund condition of the patient changed toward that of a normal person The metastatic infiltration of the lungs had regressed and epileptic seizures ceased The ECG had become closer to normal During this time the weight gain was 18½ lb and the cell water had increased by 11 lb The patient with acromegaly gained 13 lb after two months therapy

True obesity can be treated by dietary measures over weight because of a large LBM cannot

Body Compartments Their Measurement and Application to Clinical Medicine From measurements made with antipyrine of total body water content and thiocyanate measurements of extracellular water content George J Hamwi and Stuart Urbach[3] (Ohio State Univ) estimated the body composition of fat minerals intracellular water and cell solids

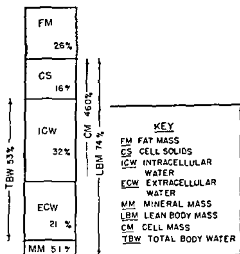


Fig 109—Total body weight portrayed as sum of individual compartments with average percentage composition given for normal persons (Courtesy of Hamwi G J and Urbach S Metabolism 2 391 403 September 1953)

(Fig 109) Forty one determinations were performed on 38 patients who were fasting and in the postabsorptive state

Five normal individuals aged 36 53 averaged 53.4% total body water 21.7% extracellular water 26.9% fat mass 5.1% mineral mass and 46.0% cell mass In five patients who were emaciated because of chronic undernutrition (Fig 110) the average content of total body water 68.8% approached the theoretical limit of 73.2% this is the value that would be expected in a fat free body The average fat mass 6.1% was extremely low and the average content of extracellular water 31.4% high The cell mass average 55.9% was the highest

(3) Metabolism 2 391-403 September 1953

Body Composition in Nutritional Edema C Gopalan P S Venkatachalam and S G Srikantia[4] (Coonoor South India) determined the body composition of patients with advanced semistarvation on admission to the hospital and after a few days of nutritional rehabilitation Plasma volume was determined by the dye method (Congo red or Evans blue) and estimations were done with a photoelectric colorimeter Sodium thiocyanate was used for estimating extracellular fluid volume The urea method of McCance and Widdowson with modifications was used for estimating total body water In the initial edematous stage it was assumed that the amount of body depot fat was negligible The difference in weight of bone minerals in the initial and final stages was negligible The weight of cellular solids was obtained as the difference between total body solids and weight of minerals After clearance of edema McCance and Widdowson s method was used in determining the various components of the body

After institution of treatment body weights actually decreased since presumably loss of weight due to edema clearance was greater than gain of tissue weight All patients had oliguria polyuria did not develop until several days after treatment was started Hookworm infestation complicated a few cases The absolute plasma volumes of the patients were lower than reported normal figures In the presence of edema correlation of body weight to plasma volume may be misleading Correlation of total body solids to plasma volume may be more reliable In the normal subject the ratio is roughly 8 In seven patients studied the mean value was 3 2 The absolute plasma volumes although less than normal were considerably raised in proportion to other tissues The absolute amount of extracellular fluid in most subjects far exceeded normal values This increase was often inapparent because the diminished body solids provided space for the accumulation of excessive extracellular fluid without producing much swelling

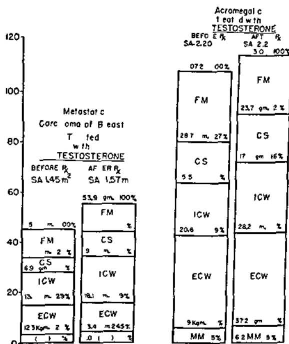
With the disappearance of clinical edema there was an absolute increase in cellular solids and a definite reduction in the amount of total body water

Influence of Potassium Salts on Efficiency of Parenteral Protein Alimentation in the Surgical Patient is described by Peggy M Frost and Jullien L Smith[5] (Los Angeles) Many

(4) M tab l m 335 342 M h 1953
(5) Ib d. pp 529 535 N mbe 1953

In the study of metabolism cell mass may be a better ref erence point than either surface area or total body water since it has been shown that in two patients treated with testoster one there was an appreciable gain in cell mass without propor tional change in surface area

In this study the assumption was made that the lean body



F g 111 —Ch ng n b dy compa tment n ab l t w ght (k l g ms) afte adm st t n f t t st e The n e n tot l b dy w te a d ll m w th t p op t o t crea e n w ght a d s rfac a (SA) s sh wn (Co tesy of Hamw G J nd U b h S M tabol sm 2 391 403 S ptembe 1953)

mass has a constant water content but it is uncertain whether this holds in pathologic states

[The physician can evaluate his patient quantitatively more effectively by relating metabolic processes to mass of functioning tissue rather than to some arbitrary measurement such as surface area weight age etc The preceding papers outline two methods of estimating lean body mass These measurements are used for differentiating obesity from muscular overdevelopment and for determining the action of an anabolic steroid such as testosterone This approach is used in the following article to describe the effects of starvation and re-alimentation —Ed]

Effects of Resistance Exercises on Nitrogen Phosphorus and Calcium Metabolism of Patients with Rheumatoid Arthritis during exacerbations of the disease were studied in two patients by appropriate analyses of diets urines and stools William S Clark Arthur L Watkins Henrick O Tonning and Walter Bauer[6] (Boston) report that although there were *no objective changes in the rheumatoid arthritis of the patients* each noted an improved sense of well being and an increased endurance which was attributed to training There was a protein anabolic effect in both patients and a decreased excretion of calcium in one These effects were also observed during the administration of testosterone While receiving testosterone one patient gained 2½ lb and about 2¾ lb during the exercise period

Although nitrogen phosphorus ratios derived from the experimental data were less than those calculated for muscle protein from balance studies and from analysis of human collagen free muscle both nitrogen and phosphorus were retained in approximate proportion of their content in muscle

Studies of muscle tissue from patients with rheumatoid arthritis have shown a decrease in myosin and collagen content but the observations in this study suggest that a mechanism exists for regeneration of muscle protein under proper stimulation The absence of increases in urinary nitrogen phosphorus and calcium excretion in both patients and the failure of the urinary 17 ketosteroid level to rise in one indicate that the exercises did not initiate the usual adrenocortical response to stress The metabolic responses to physical exertion were similar to those observed by others in normal subjects during restoration of physical activity after prolonged immobilization

Clinical Spectrum of Obesity J H Sheldon[8] points out that experimental damage to the medial nuclei of the hypothalamus results immediately in so voracious an appetite that the rat for example may treble its normal food intake with consequent rapid weight gain with fat accounting for possibly 70 % of the weight Conversely damage to the lateral nuclei leads to total loss of appetite

A close parallel in human nutrition was found in maternal obesity Figure 112 is a composite of 19 records of weight

(6) J Cl I est. 33 505 509 Ap l 1954
(8) B t M J 140 1404 D 6 1953

reports show a parallel loss of potassium with a breakdown in cellular protein The present study demonstrates the need for potassium when nitrogen and caloric requirements are *met to obtain increased glycogen deposition in the liver and* enhanced nitrogen utilization in depleted patients

The 10 men used in this study aged 31 70 and weighing 43 82 kg were divided into four groups No food was given orally Urine was collected over a 24 hour period No nitrogen was lost through defecation Electrolyte intake and weight were recorded Nitrogen equilibrium was assumed to be achieved when the nitrogen content of the ingested protein was equal to the nitrogen recovered from the urine Positive nitrogen balance was achieved when a definite retention was present in the tissues

Group 1 patients were given 3 100 calories and 28 Gm of nitrogen Various amounts of potassium and 120 mEq sodium chloride were added to the infusion daily Group 2 patients were given 3 104 calories 12 Gm nitrogen and 40 80 mEq potassium daily with sufficient sodium chloride to replace losses due to gastric suction The one patient in group 3 was given daily 3 200 calories 16 Gm nitrogen 120 mEq sodium chloride and 40 mEq potassium chloride Group 4 patients were given 2 800 calories 16 Gm nitrogen and 120 mEq sodium chloride daily During one five day period no potas sium was given but during the following five days each pa tient received 80 mEq daily

Results are given for a representative patient in each group In the group 1 patient negative nitrogen balance oc curred when 20 mEq or less potassium was given Optimal nitrogen retention was attained when potassium exceeded 4 mEq /Gm nitrogen infused The group 2 patient was in nega tive nitrogen balance when given 40 mEq potassium and 70 Gm nitrogen daily When he was given 80 mEq potassium chloride with the same amount of nitrogen he showed an im mediate positive potassium and nitrogen balance The group 3 patient was maintained on 40 mEq potassium daily and was in a positive potassium and nitrogen balance for the entire study period In group 4 the patient was in a constant nega tive potassium and nitrogen balance He showed marked nitro gen retention beginning with the first day of adequate potas sium therapy

increased appetite through interference with the satiety mechanism which may be normally actuated by sensitivity in the appropriate hypothalamic cells to metabolites in the blood stream possibly glucose Adrenal steroids may influence the appetite by direct effect on the hypothalamus

[There are probably many causes of obesity This study suggests an explanation for postpartum obesity however in addition to these factors the compelling emotional forces which also operate at this time may be important The distinction between the voracious appetite of the anabolic phase and the normal food intake when a plateau is reached is useful for effective weight reduction caloric intake must usually be reduced below the normal level —Ed]

Weight Reduction Study of the Group Method, Preliminary Report H I Harvey and W D Simmons[9] (Berkeley Calif) studied the effectiveness of a group approach to the problem of weight reduction

PROCEDURE —Each applicant had repeated physical examination laboratory tests nutrition interviews and psychologic tests Attendance at 16 weekly meetings adherence to the prescribed diet and availability for follow up were emphasized The 109 women were divided into two groups A nutritionally centered approach was led by a health educator and a nutritionist and a psychologically centered approach was led by an instructor of social group work and a psychiatric social worker The groups were then divided into those above and those below 40 Each leader had both an older and a younger group Every individual in each group was given a 1 000 calorie diet with 80 Gm protein 80 Gm carbohydrate and 40 Gm fat

Of 93 patients who attended more than four meetings 77 lost 10 lb or more of these 46 lost 20 lb or more The maximum individual weight loss was 51 lb Only one did not lose none gained Of the remaining 15 who lost 1 10 lb 11 lost more than 5 lb The total weight lost by the 93 was 1 730 lb There was no difference in weight loss between the types of groups

Of 74 patients contacted at the end of one year 10 continued to lose 1 21 lb 3 maintained their weight and 25 gained 1 28 lb The 17 that lost less than 10 lb during the project subsequently lost 2-40 lb

The outstanding characteristic of a group is that they react interpersonally thus promoting self therapy Except for research purposes perhaps anyone provided he is people minded sympathetic to the problem and assisted by instruction can work successfully with a group for weight reduction Knowledge of dietary needs must be authoritatively provided

(9) Am J M S 2 5 623 5 J 19 3

gain over different but definite periods The rates of gain by the different women appear to follow a common path After delivery *weight gain began with the same dramatic rapidity* gradually tapering off until a steady state was reached Any subsequent gain was extremely slow The period of rapid gain was accompanied by excessive appetite with no feeling of satiety however much was eaten As the rate of weight gain slowed the intervals before hunger reappeared seemed to lengthen It was as if a satiety mechanism which was nil at the start were gradually enhanced as the weight approached a set target

When steady weight was reached many patients were not taking excessive food The lack of correlation between caloric

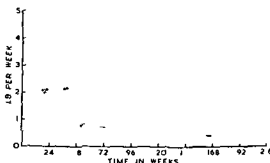


Fig 112—Rec d f w ght ga (n lb/week) n m t l of ty (Co t y of Sheldo J H B t M J 2 140 1404 D 26 1953)

intake and body weight can be explained by a high caloric earlier diet and a diminution in physical activity

The hypothalamus may also play a role in the obesity that follows inflammation or injury to the lower brain to fracture of the base or to subarachnoid hemorrhage The syndrome of periodic somnolence and morbid hunger (Kleine Levin) is a link with associated alterations in hypothalamic function rather than with structural damage

A cortical factor must be assumed in the obesity that follows frontal leukotomy that is a response to emotional states and possibly that which follows abstinence from tobacco Endocrine changes that accompany obesity require careful interpretation since they may derive from rather than be causative of it

It has been suggested that hypothalamic damage leads to

The first patient presented the clinical syndrome of fulminating malignant hypertension with retinopathy the second had a moderately severe hypertension and it is not likely that the third patient would have sought medical aid or that the diagnosis would have been made if tumors had not been diagnosed and removed from his two sisters

[*The bilateral distribution of these tumors is unusual The beneficial effects of cortisone postoperatively are well illustrated Pre treatment with cortisone before the operation would have anticipated the probability that this hormone would be needed and offered protection throughout the surgical procedure —Ed*]

Further Study of Utilization of Dietary Glycine Nitrogen for Uric Acid Synthesis in Gout A previous study revealed that three times as much of the administered glycine nitrogen could be recovered in urinary uric acid in the gouty subject as in two normal controls The gouty subject used in the initial study was selected because of his excessive basal urinary uric acid excretion Jean D Benedict T F Yu Edward J Bien Alexander B Gutman and Dewitt Stetten Jr (Mount Sinai Hosp New York City) report on three gouty subjects one excreting excessive the other two normal quantities of uric acid in the urine under prescribed dietary conditions

Isotopic glycine (N^1 = 60 5 atom % excess) 100 mg /kg body weight was fed with breakfast to each subject All subjects were on a restricted protein diet for 5 10 days before administration of glycine and throughout the period of urine collections

Two gouty subjects D R and H G had higher concentrations of isotope than the normal controls The initial rise was more rapid as was the subsequent decline in N^{15} abundance From quantity of N^1 fed quantity of uric acid excreted in each day s urine and N^{15} concentration in this uric acid the percentage of administered dose of N^{15} excreted as uric acid was calculated H G and D R eliminated a larger fraction of the glycine nitrogen as uric acid than the normal subjects Accumulated excretions of dietary glycine nitrogen as urinary uric acid were three to four times normal in D R and H G in nine days following feeding of glycine N^{15}

In H G and D R there was unequivocal evidence for abnormally rapid incorporation of dietary glycine nitrogen into uric acid In the other two patients this effect was either unimpressive or absent A good rank order correlation was

(2) J Cl I st 32 775 777 A gu t 1953

Familial Pheochromocytoma Report on Three Siblings with Bilateral Tumors which were successfully removed is given by Grace M Roth Nicholas C Hightower Jr Nelson W Barker and James T Priestley[1] (Mayo Clinic)

CASE 1 —Girl 18 had blood pressure of 190/150 on admission Examination of the optic fundi revealed bilateral papilledema with large exudates and hemorrhagic areas Routine laboratory and x ray findings were normal Piperoxan and regitine® tests indicated a pheochromocytoma On operation a multilobulated tumor was found in each adrenal gland Marked elevations of blood pressure which occurred during operation were satisfactorily controlled by intra venous administration of 10 mg piperoxan Immediately after re moval of all tumor tissue the patient went into vascular collapse which was controlled by continuous intravenous administration of l arterenol and epinephrine This therapy was continued for 27 hours Because considerable adrenal tissue had been removed at operation 200 mg cortisone was administered intramuscularly during surgery and 75 ml aqueous adrenal cortex extract was added to the intra venous fluids given postoperatively

CASE 2 —Woman had blood pressure of 190/130 on admission The retinal arterioles showed slight sclerosis general narrowing and focal constrictions In view of a clinical history suggestive of pheochromocytoma and positive pharmacologic tests surgery was undertaken bilateral pheochromocytomas were found and removed Because of the large amount of adrenal tissue removed at operation 30 ml whole adrenal cortex extract was given intravenously at once and 20 ml was given intramuscularly The precipitous drop in blood pressure after the blood supply of the second tumor was interrupted was controlled by continuous intravenous administration of epinephrine and l arterenol for 48 hours

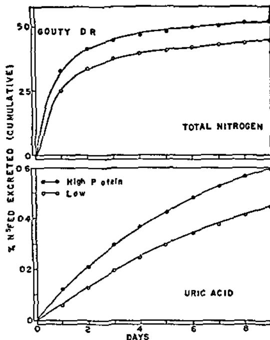
CASE 3 —Man 25 a brother of the two other patients had transient hypertension with positive pharmacologic tests for pheo chromocytoma On operation two tumors of the right gland and one on the left were removed Cortisone 200 mg was given at once intramuscularly and was continued in diminishing amounts to the fifth postoperative day During operation excessive increases in blood pressure were controlled by phentolamine intravenously Im mediately after operation and for 60 hours thereafter epinephrine and l arterenol were given intravenously

Pheochromocytomas may be multiple malignant bilateral and located elsewhere than in the adrenal gland At operation both adrenal glands should be explored and a search for pos sible ectopic location made

(1) A M A Arch Surg 67 100 109 July 1953

acid synthesis was demonstrable when the consumption of dietary protein was enhanced

METHOD—The subjects were one gouty man who was known to excrete excessive quantities of uric acid in the urine and to incorporate glycine N^{15} at an augmented rate when maintained on a low protein diet and one normal man Experiments were carri d



F g 114—E t f N^{15} ty t tal tr g d ri d by g ty bject h gh a d l w p t n d t C m l t per t g f t tal d f N^{15} t d h been pl tt d (Cou t y f B E H t l J Cl I t 32 7 8 780 A gu t 1953)

out while the subjects were on a low purine diet and on the same diet fortified with lonalac® (to increase the protein intake significantly) After an interval of 10 12 months to insure the ab ence of detectable isotopic enrichment the experiments were repeated Glycine N^{15} was administered (100 mg /kg body weight)

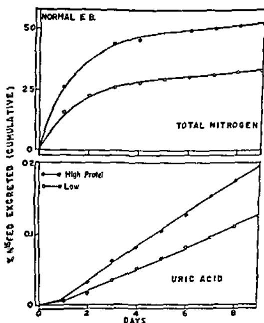
Uric acid excreted in the early period by both subjects was richer in isotope when they were on a high protein regimen There was a more rapid decline in isotope concentration

noted between the daily excretion of uric acid in the urine and per cent of ingested isotope appearing in urinary uric acid

The possibility was entertained that the gouty subject might be overproducing uric acid Therefore the value of the miscible pool of uric acid was determined in one patient and was found (1 500 mg) not to deviate sufficiently from the normal (1 100 mg) to permit the conclusion that impressive overproduction of uric acid was occurring in this patient

[It is possible to have gout without increased urinary uric acid excretion increased uric acid synthesis or an increased miscible uric acid pool in the body —Ed]

Relation of Dietary Nitrogen Consumption to Rate of Uric Acid Synthesis in Normal and Gouty Man Edward H Bien T F Yu Jean D Benedict Alexander B Gutman and Dewitt Stetten Jr [3] (Mount Sinai Hosp New York City) attempted to ascertain whether an increase in the rate of uric



F g 113 —E t f N15 u y t tal t og n d c acid by n mal b t h gh a d a low p t n d et Cum l t p c tag f t t J d f N15 c ted h been plott d (C te y f B E H t l J Cl n I t 3 7 878) A gu t 1953)

(3) J Cl In e t 3 7 8 80 A g t 1953

had had only episodes of mild erythema frequently without discomfort at one to two month intervals which usually subsided spontaneously in less than 24 hours Occasionally supplementary colchicine was required The nodules in the fingers gradually disappeared Serum uric acid level remained unaltered ranging from 7 to 10 mg /100 ml He continued to take 50 mg cortisone daily for 22 months

Effect of Phenylbutazone (3,5 Dioxo 1,2 Diphenyl-4 N Butylpyrazolidine) on Renal Clearance of Urate and Other Discrete Renal Functions in Gouty Subjects was studied by Tsai Fan Yu Jonas H Sirota and Alexander B Gutman[5] (New York City) In 10 gouty subjects receiving phenylbutazone intravenously in doses of 12 27 mg /kg body weight C urate rose from a mean control value of 6 3 cc / minute to a mean peak of 19 3 cc /minute and C urate/C_{IN} × 100 rose from a mean control of 6 04 to 19 5 within two hours Elevation of C urate/C_{CR} continued 20 22 hours All 10 subjects had uricosuria which appeared to correlate with dosage

In two patients receiving slow intravenous infusions of phenylbutazone elevations of C urate/C_{IN} were first noted at plasma phenylbutazone concentrations of about 10 mg /100 ml Stepwise elevation of C urate/C_{IN} occurred with rising drug concentrations in the plasma Eight gouty subjects were given phenylbutazone orally in dosages of 800 mg /day Seven had increased urinary urate excretion but duration and magnitude of this response were variable All subjects exhibited a decrease in plasma urate concentration In three inconsistency was observed between degree of uricosuria and decline in plasma urate concentration

The glomerular filtration rate (GFR) was unaffected in 8 of 13 gouty subjects following intravenous administration of phenylbutazone 5 exhibited a slight depression in GFR This effect continued 20 22 hours in three subjects The most profound depression in GFR (80 6-60 6 cc /minute) occurred in the subject receiving the largest dose—35 mg /kg body weight

Depression in C_{PAH} from a mean control value of 495 cc / minute to a mean minimal value of 326 cc /minute occurred in 10 subjects receiving phenylbutazone intravenously This effect appeared rapidly and was sustained throughout the

(5) J Cl I t. 32 1121 113 N mbe 1953

in uric acid in the latter period of the experiment This confirms the indication that incorporation of glycine nitrogen into uric acid is more rapid when a high protein diet is given These data, together with the total N^{15} excretion data have also been plotted as *cumulative percentage of the N^{15} fed* which was excreted as total urinary nitrogen and as uric acid (Figs 113 and 114) In both subjects an appreciably greater fraction of administered glycine nitrogen was excreted in the total nitrogen of the urine when a high protein diet was fed The increase in total N^{15} excretion produced by dietary change is roughly paralleled by the increase in uric acid N^{15} excretion In the normal subject the percentage of the total urinary N^{15} found in uric acid appeared to be independent of the quantity of protein ingested In the gouty subject a considerably larger percentage of excreted N^{15} was recovered in uric acid (1 02 and 1 16 on low and high protein diets) When *on a diet fortified with protein both subjects incorporated* dietary glycine nitrogen more rapidly into uric acid than when on a low protein diet

Dietary protein should be restricted in situations such as *tophaceous gout when the rate of uric acid synthesis* should be reduced to a minimum

Suppression of Manifestations of Gout with Continuous Cortisone Therapy Augustus E Anderson Jr [4] (Tulane Univ) presents one case

Man 51 hospitalized on April 22 1950 with a painful swollen left ankle had recurrent attacks of acute joint symptoms which predominantly affected the wrists elbows knees ankles feet and great toes since 1944 He had nontender firm subcutaneous nodules on the medial aspect of the ring finger and thumb of the right hand Serum uric acid level was 11.2 mg /100 ml After colchicine therapy joint symptoms subsided Diagnosis was gout Despite a low purine diet daily prophylactic administration of sodium salicylate and the use of colchicine he continued to have recurrent joint symptoms during the subsequent year

On May 15 1951 he was started on 300 mg cortisone daily Within 24 hours there was 50% subjective improvement and within five days there was complete disappearance of all signs and symptoms of joint disease With a maintenance dose of 150 mg daily he had mild *recurrent acute joint symptoms at intervals of* about one week that were easily controlled with nontoxic doses of colchicine Since August 15 when the dose was reduced to 50 mg daily he

(4) Am J Med 16 29 94 February 1954

of sodium bicarbonate a flavoring agent and sodium sulfite as a preservative made up to ½ fluidounce (15 cc) The mixture was given three times daily with doses equally spaced through the 24 hours Total daily dose varied from 60 140 gr (4 93 Gm) During continuous salicylate therapy there was improvement in the pain discomfort and stiffness of the joints

CASE 7—Man 45 after therapy for seven months could walk 2 miles for the first time in 10 years He worked regularly and for 18

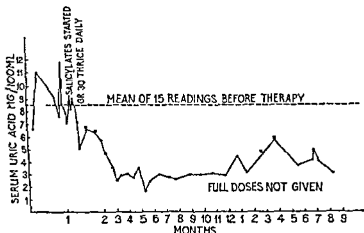


Fig 115—S rum uri d lev l d ri g 19 m th of od m l yl te th py (C t y f M F G W Q t J M d. 2 331 346 J 20 1953)

months was free from continuous pain He had only occasional and minor acute attacks

CASE 18—Man 51 was totally incapacitated with multiple joint pains for nine months Pain rapidly lessened with therapy and after one year he was able to walk up to 12 miles a day

There was no case of tophi enlargement and in two cases conspicuous tophi disappeared In three cases tophaceous ulcerations healed

CASE 16—Man 49 had tophi that were removed surgically Prior to therapy he had about 15 tophi on his fingers some the size of a cherry which interfered with holding a pen Six months after starting therapy all tophi had disappeared Figure 115 shows his response to salicylates

During salicylate therapy there was no deterioration in

period of observation In two subjects so studied the Tm_{PAH} fell from control values of 75 4 and 61 4 mg /minute to 12 9 and 14 mg /minute respectively

In three subjects phenylbutazone given intravenously in doses of 800 mg /day produced depressions of C_{Na}/C_{Cr} and C_{Cl}/C_{Cr} without appreciable changes in C_K/C_{Cr} and C_P/C_C There was significant sodium and chloride retention

Simultaneous administration of phenylbutazone and benemid® did not result in marked inhibition of the uricosuric effect of either drug

The study indicates that the principal renal effects of phenylbutazone are on tubular transport mechanisms inhibiting reabsorption of urate and secretion of PAH and increasing *the reabsorption of sodium and chloride*

Despite its uricosuric action phenylbutazone is not recommended for protracted use as a uricosuric agent in chronic gout since its enhancement of urinary urate excretion is distinctly less than that of equivalent doses of benemid® and it is much more prone to produce serious toxic reactions

Studies in Gout, with Particular Reference to Value of Sodium Salicylate in Treatment are described by F G W Marson[6] (Univ of Birmingham) In the normal human adult approximately 90% of urate passing in the glomerular filtrate is reabsorbed by the tubules This percentage increases with a rise in plasma uric acid levels If plasma urate is artificially increased in human subjects a maximum tubular transport capacity occurs at about 15 mg /minute Such a reabsorption rate requires a plasma urate level in excess of 15 mg /100 ml which is rarely exceeded in gout Many gouty persons have renal impairment with reduction of glomerular filtration rate

Eight men with gout were placed alternately on low purine and high purine diets for 7 11 days each Approximate values were 0 2 and 0 5 Gm purine nitrogen respectively In only one case did the change from low purine to high purine diet fail to produce a rise in the serum uric acid level The mean rise for the group was 1 3 mg /100 ml

Sodium salicylate was administered continuously for up to 34 months in the treatment of 29 patients with chronic gout It was dispensed as a fluid containing an equal quantity

(6) Q rt. J Med. 331 346 J 0 1953

associated severe hypertrophic arthritis Ochronosis is seldom associated with herniated intervertebral disk but one case of alkaptonuria associated with hyperuricemia has been reported Arthritis may involve hips knees and shoulders with narrowing of the joint space and spur formation Calcific deposits may be found in quadriceps tendons Small joints are seldom involved Pigmentation may appear in the joint cartilages but is often observed first in the concha and antihelix and only later in the tragus The nasal cartilage is usually involved It is important to differentiate small patches of scleral ochronosis from melanosarcoma

Chemical tests for diagnosis and therapy of alkaptonuria or ochronosis are nonspecific

Hereditary Ochronosis Pathologic Changes Observed in Two Necropsied Cases are reported by Louis Lichtenstein and Leo Kaplan[8] (Univ of California Los Angeles) A typical case is summarized

Man 52 was hospitalized for dyspnea orthopnea and edema of both feet and ankles Mitral insufficiency and aortic stenosis were suggested Roentgen studies disclosed severe arthritis of the knees hips and spinal column prominent marginal exostoses along the vertebral column and disruption with increased density of intervertebral disks

The autopsy protocol briefly mentioned the blackening in costal cartilages the lining of the sternoclavicular joint and the intervertebral disks In sections of the lung dark brown pigmentation of bronchial cartilages and their perichondria was noted

Skin pigmentation is expressed most obviously by ochronosis with skeletal connective tissues bearing the brunt of such pigment deposition The bones themselves except for the joints and the periosteal investment are only affected to limited extent Near the involved joints and disks and adjacent to the periosteum are found trabeculae with the osteoblasts and their lacunae stuffed with pigment and with a matrix having brownish discoloration Reactive villous synovitis marginal exostoses conspicuous subchondral sclerosis and other changes of advanced osteoarthritis appear Although the mechanism that leads to the development of intra articular fracture fragments differs the sequence of events resembles that in a Charcot joint Arthritic manifestations elsewhere and ochronotic ankylosing spondylitis appear simultaneously The

(8) Am. J P th. 30 99 125 J n F b 1954

radiologic appearance and four patients improved There was *recalcification and a decrease in the size of areas of bone replacement* Maintenance of serum uric acid at normal levels did not necessarily prevent acute gouty attacks

Sodium salicylate was prescribed initially in a daily dose of 90 gr (6 Gm) and symptoms of salicylism usually resulted Unless attacks were severe patients were encouraged to continue for about a month when most tolerated the drug well Hemorrhagic manifestations were not observed Of 200 estimations performed in 16 patients, a fall in prothrombin *concentration to below 50% of normal was noted 12 times* (6%) and 3 (1 5%) were below 25% of normal When the prothrombin concentration fell below 25% of normal 10 mg vitamin K orally twice a day was prescribed until normal values returned

[It is sometimes forgotten that salicylates can produce all of the beneficial effects of probenecid. Unfortunately the dose level necessary for this effect is often in the toxic range —Ed.]

Alkaptonuria and Ochronosis Report of Five Cases Occurring in an American Family is presented by Roger L *Black John F Lowney and Paul M Duffy*[7] *(Baltimore) The* following case is illustrative

Man 37 was hospitalized for low back pain after a slight injury on shipboard The pain neither radiated nor was progressive Bluish discoloration of the ears began at age 20 and a reducing substance had been found in the urine some seven years later After many routine examinations he had been told about the sugar in his urine Laboratory tests disclosed alkaptonuria Spinal x ray disclosed hypertrophic changes around the articular margins of the lumbar *vertebrae and calcification of intervertebral disks and longitudinal* ligaments

Alkaptonuria usually inherited as a mendelian recessive trait is twice as common among women It can be recognized by the fact that the urine turns black on exposure to air and stains clothing It usually appears in childhood Because of the presence of a reducing substance in the urine diabetes at some time in life is suspected

The life span in alkaptonuria is normal Ochronosis reportedly develops in about half of the afflicted people Arthritic symptoms appear usually during the 3d or 4th decade Spinal x rays of all five patients *in this series disclosed de*generation, calcification or both of intervertebral disks and

(7) A M.A. Arch. Int. Med. 93 86 January 1954

does not have porphyria but porphobilinogen is usually absent Porphyric urine fluoresces on exposure to ultraviolet light Spectroscopy confirms the presence of porphyrins in the acute or chronic stage of the illness In the latent stage diagnosis is difficult and depends on a detailed history of nervous breakdowns abdominal pains operations health during pregnancy drug taking blistering of skin death from paralysis in a relative and history of red urine

After an operation many patients with porphyria complain of weakness which may be regarded as hysterical until a lower neuron type of paralysis develops Their reflexes disappear their pupils dilate and the heart rate is rapid As the paralysis progresses the mental symptoms and abdominal pains lessen Prognosis should be guarded There are impaired liver function and leukocytosis but no characteristic changes in the ECG If the patient recovers the peripheral neuritis may persist for months

Treatment in the acute stage requires good nursing Methionine vitamin B_{12} vitamin B complex and vitamin C have been given Corticotropin appears to be of some value Barbiturates thiopentone anesthesia and sulfa drugs must be avoided If one case of porphyria is diagnosed it is the physician s responsibility to go fully into the family history to discover other undiagnosed cases in order to prevent much suffering and unnecessary operations

essential basis is heavy impregnation of intervertebral disks with ochronotic pigment

Pigment deposition in the blood vessels relates to accentuated arteriosclerosis and to the development of valvular defects especially aortic stenosis In one patient coloration of the annulus and of the commissural junctions of the pulmonic valve was noted the annulus of the mitral valve was irregularly pigmented and calcified In the aortic valve the cusps and annulus and the sinuses of Valsalva were intensely pigmented Fusion of the commissures and stenosis of the valve were also noted

Hereditary ochronosis results in a specific type of disabling arthritis and ankylosing spondylitis Calcific aortic stenosis was observed Other deleterious effects were severe arteriosclerosis ochronotic nephrosis deposition of pigment in the pancreatic islets and formation of pigment calculi in the urinary tract

[Alkaptonuria and ochronosis is not a benign disease Serious disability may result from arthritis cardiovascular lesions and pigment stone formation.—Ed]

Porphyria, in the families studied by Geoffrey Dean[9] (Port Elizabeth South Africa) was inherited as a mendelian dominant Many porphyrics have various pains particularly abdominal which lead to drug addiction futile laparotomies and diagnosis of neurosis In the acute attack abdominal pain may lead to a diagnosis of appendicitis intestinal obstruction or other abdominal emergency Minor injuries appear to precipitate blistering and ulceration of the skin which heal slowly The ulceration is more common during pregnancy when the patient s condition is much worse Conjunctivitis is common There may be small pigmented spots in the retina that fluoresce in ultraviolet light

The acute attack generally follows drug taking anesthesia or occurs *spontaneously during pregnancy* If paralysis has developed poliomyelitis Guillain Barre syndrome and hysteria must be excluded Porphyrins are present in the urine but in the chronic or latent stages the usual tests for porphyrins may have negative results Presence of porphobilinogen is shown by the Watson Schwartz test An increased excretion of porphyrins may also occur in hepatitis in a patient who

(9) Brit. M J 2 1291 1294 Dec. 12 1953

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